New Strategies for Synthesis with Boronate Esters

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Ph.D. Thesis

University of Durham
Department of Chemistry
2013

Statement of Copyright

Declaration

The work described in this thesis was carried out in the Department of Chemistry at Durham University and Glaxosmithkline R&D, Medicines Research Centre, Stevenage, between October 2008 and December 2012, under the supervision of Prof. Patrick G. Steel, Prof. Todd B. Marder, Dr. Aoife C. Maxwell and Dr. Lena Shukla. All the work is my own work, unless otherwise stated, and has not been submitted previously for a degree at this or any other university.

Hazmi Tajuddin

Acknowledgements

First and foremost, I would like to thank my supervisors Prof. Patrick G. Steel, Prof. Todd B. Marder, Dr. Aoife C. Maxwell and Dr. Lena Shukla. Their encouragements, guidance and support throughout my studies have made these last 4 years a challenging but an enjoyable and fulfilling experience.

Many thanks to Dr. Alan Kenwright and Catherine Heffernan from the NMR service. Their willingness to help is second to none.

I would also like to thank all past and present members of CG1 and CG52, with special mentions to Dr Jonathan Sellars for his all his help, Dr John Mina for useful discussions, Marvis for his unique brand of humour, Meng Guan for brushing up my Malay, Bianca for being cheerful all the time, Marie-Hélène for feeding my obsession with badminton, Nim for her cooking, Andrew for one of the best holidays ever, Hannah for making me cakes, Henry for his tolerance, Emily for encouraging my singing antics in the lab, and Neil 'Guvnor' Sim for his continued interest in my work. Special thanks also to 'Skipper' Chris, Scott and Chris 'Brown Sauce' for their unwavering support of FFF (Fast-Food-Friday).

And last, but by no means least, I'd like to thank my family, for their love and support and for always being there for me. I love you all to bits!

Conferences and Seminars Attended

2009

13/1/09 *42nd Sheffield Stereochemistry* - Sheffield (**attended**)

6/5/09 *Pre-Grasmere Meeting and RSC Endowed Lecture Symposium in honour of John Hartwig* - York (**attended**)

7/10/09 *Young Academics Symposium* – GSK**,** Stevenage, UK – (**attended**) 9/10/09 *2nd Array Chemistry Symposium* – GSK, Stevenage, UK (**talk**)

17/12/09 *Complex Natural Products as a Driving Force for Discovery in Organic Chemistry* – GSK, Stevenage, UK (**attended**)

2010

17/3/10 *C-H Activation in Organic Synthesis* – GSK, Stevenage, UK (**attended**)

15/4/10 *Medicinal Chemistry Seminar Programme* – GSK, Stevenage, UK (**presented**)

24/5/10 GSK Novel Synthetic Methods Symposium – Stevenage, GSK (**attended**)

1/9/10 *3rd Array Symposium* – GSK, Stevenage, UK (**talk**)

13-15/9/10 *Royal Society of Chemistry Dalton Discussions* – Durham University, Durham, UK (**attended**)

20-21/9/10 *Eli Lilly's 8th European Drug Discovery Workshop* – Eli Lilly, Erl Wood, UK (**attended**)

2011

15/6/11 *Durham Postgraduate Symposium* – Durham University, Durham, UK (**poster**)

7/7/11 *Chemistry Symposium* – University Malaysia Sarawak, Kuching Malaysia (**talk**)

25/10/11 *NORthern Sustainable Chemistry Network Seminar* – Kings Manor, York, UK (**poster**)

2/11/11 *Royal Society of Chemistry/Society of Chemical Industry Challenges in Catalysis III* – Burlington House, York, UK (**poster**)

15-18/12/11 *Junior National Organic Symposium Trust* – National Institute of Science Education and Research, Mohali, India (**talk**)

2012

25-29/3/12 *243rd American Chemical Society National Meeting and Exposition* – San Diego Convention Centre, San Diego, USA (**talk**)

12/4/12 *23rd Society of Chemical Industry Regional Postgraduate Symposium* - Leeds University, Leeds, UK (**talk**)

Publications

1. **"One-Pot" Tandem C-H Borylation/1,4-Conjugate Addition/Reduction Sequence**

   Tajuddin, H.; Shukla, L; Maxwell, A. C.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2010**, *12*, 5700

2. **Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides**

   Yang, C. T.; Zhang, Z. Q.; Tajuddin, H.; Wu, C. C.; Liang, J.; Liu, J. H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528

3. **Iridium-catalyzed C-H borylation of quinolines and unsymmetrical 1,2-disubstituted benzenes: insights into steric and electronic effects on selectivity**

   Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. *Chemical Science* **2012**, *3*, 3505

Abstract

Aryl and alkyl boronic acids and their derivatives have a broad variety of applications, ranging from uses in medicines to cross-coupling partners in modern organic synthesis. This thesis presents the work undertaken in both the synthetic and application aspects of this important class of synthetic intermediates.

Chapter 1 gives a brief overview on the bonding and physical properties of boronic acids, their synthesis and applications.

Chapter 2 shows that the activation of C-H bonds in the iridium-catalysed borylation of arenes is contingent on C-H acidity in the absence of steric effects, allowing for the prediction of regiochemistry through a simple ^{1}H NMR analysis of the starting material.

Chapter 3 shows that the high electronic barrier hindering the borylation of C-H bonds alpha to a pyridyl nitrogen can be overcome through steric effects, and that the resultant α-pyridyl boronate can be used, *in-situ*, in Suzuki-Miyaura cross-coupling reactions.

Chapter 4 describes the development of C-H borylation/1,4-conjugate addition sequence, for the synthesis of β-aryl ketones and also the corresponding alcohols under reducing conditions.

Chapter 5 describes the development of a new methodology for the preparation of alkyl boronate esters through copper-catalysed borylation of alkyl halides and *pseudo*halides.

Abbreviations

Å	ångstrom
acac	acetoacetyl
Ac	acyl
aq.	aqueous
Ar	aryl
ASAP	atmospheric pressure solid analysis probe
Bn	benzyl
B_2neop_2	bis(neopentyl glycolato)diboron
Boc	*tert*-butoxycarbonyl
B_2pin_2	bis(pinacolato)diboron
bpy	2,2'-bipyridine
ca.	*circa*
cat	catecholato (1,2-$O_2C_6H_4$)
cat.	catalytic
cf.	confer
CMD	concerted metalation-deprotonation
cod	1,5-cyclooctadiene
coe	cyclooctene
conc.	concentrated
conv.	conversion
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl

COSY	correlation spectroscopy
cy	cyclohexyl
dba	dibenzylideneacetone
DBDMH	1,3-dibromo-5,5-dimethyldantoin
DCDMH	1,3-dichloro-5,5-dimethyldantoin
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEM	diethoxymethane
DIBAL	di-*iso*butyl-aluminium hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dmpe	1,2-bis(dimethylphosphino)ethane
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenyl-phosphino)ferrocene
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
ee	enantiomeric excess
eg	ethylene glycolato (-OCH_2CH_2O-)
EI	electron impact

eq.	equivalents
Et	ethyl
etc.	*et cetera*
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron-withdrawing group
exp.	experimental
FG	functional group(s)
FID	flame ionisation detetor
GC-MS	gas chromatography-mass spectrometry
h	hour
HBcat	catecholborane
HBpin	pinacolborane
HMBC	heteronuclear multiple bonds correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
Ind	indenyl
IPA	isopropanol
Ipc_2BH	diisopinacocampheylborane
^{i}Pr	*iso*-propyl
IR	infra-red

L.A.	Lewis acid
LC-MS	liquid chromatography-mass spectrometry
LiHMDS	lithium hexamethyldisilazide
lit.	literature
M	Molar
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
Mes	mesitylene
MIDA	methyliminodiacetic
mg	milligram
min	minute
mL	millilitre
mmol	millimole
m.p.	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
MVK	methyl vinyl ketone
µW	microwave
m/*z*	mass/charge ratio
N	normal
nbd	2,5-norbornadiene

neop	neopentylglycolato (-$OCH_2CMe_2CH_2O$-)
^{n}Bu	*iso*-butyl
^{n}Hex	*iso*-hexyl
ni	not isolated
[Ni]	nickel complex
^{n}Oct	*iso*-octyl
NOESY	nuclear Overhauser effect spectroscopy
NMR	nuclear magnetic resonance
nr	no reaction
[Pd]	palladium complex
ppm	parts per million
^{n}Pr	*iso*-propyl
OAc	acetate
OATS	oxidatively added transition state
OTf	triflate
OTs	tosylate
Oxone®	potassium peroxymonosulfate
Ph	phenyl
pin	pinacolato (-$OCMe_2CMe_2O$-)
PPh_3	triphenylphosphine
PS	polymer-supported
quant.	quantitative
rac	racemic

ref.	reference(s)
[Rh]	rhodium complex
r.t.	room temperature
Si-SMAP	silica-supported mono alkyl phosphine
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TC	thiophene-2-carboxylate
TLC	thin-layer chromatography
^{t}Bu	*ter*t-butyl
temp.	temperature
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
tert	tertiary
THF	tetrahydrofuran
TIC	total ion current
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TON	turnover number
Ts	tosyl
UV	ultra-violet
vs.	*versus*
w.r.t.	with respect to

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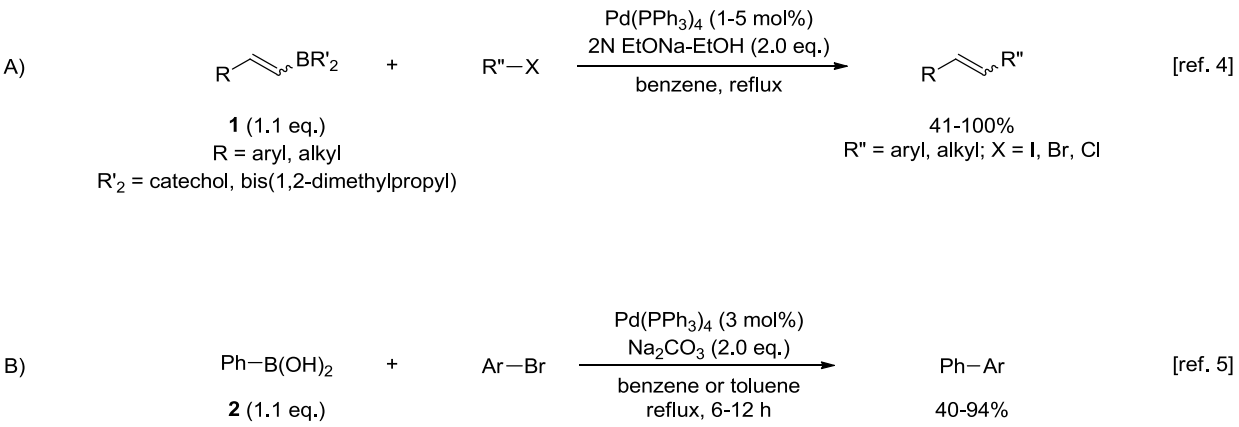
Chapter 1 - Boronic Acids and their Derivatives: Bonding and Physical Properties, Preparation Methods, Chemistry and Applications

1.1 Introduction and Background

Although the first boronic acid was isolated by Frankland in 1860 through atmospheric oxidation of triethylborane obtained from treatment of diethylzinc with triethylborate,[1-3] it was not until 1979 that chemists began to realise the power of boronic acids as synthetic building blocks. This followed Suzuki's and Miyaura's pioneering work on the palladium-catalysed cross-coupling reactions of alkenylboranes (**1**) and vinyl and aryl boronic acids and esters (**2**) with aryl halides (***Scheme 1***).[4,5] The collective impact of these publications has been enormous, as exemplified by over 1500 citations and the award of 2010 Chemistry Nobel prize to Professor Suzuki.



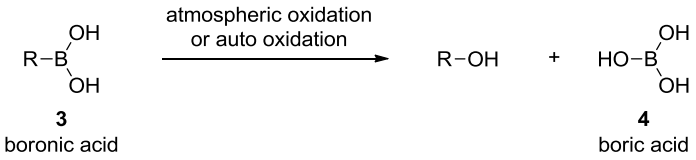
Scheme 1. First reports on the palladium-catalysed cross-coupling reactions.

Subsequently, the use and application of boronic acid derivatives has become one of the key strategies in modern organic synthesis. Reflecting this, new methods for the generation and reaction of boronic acid derivatives remain in great demand. This thesis describes work directed towards this objective and is divided into four main chapters. Chapter 2 describes

the synthesis of aromatic boronate esters through iridium-catalysed aromatic C-H borylation methodology by exploring the regioselectivity of this transformation. Chapter 3 deals with developing strategies for the synthesis of electron-deficient heterocyclic aromatic boronate esters. Chapter 4 focuses on the development of 'one-pot' sequences, combining the efficiency of the iridium-catalysed borylation with the diverse chemistry of boronic acids. Finally, Chapter 5 discusses synthetic methodologies for the preparation of alkylboronic acids. The remainder of this chapter will give a short overview of the bonding and physical properties of boronic acids, their synthesis and applications.

1.2 Bonding and Physical Properties

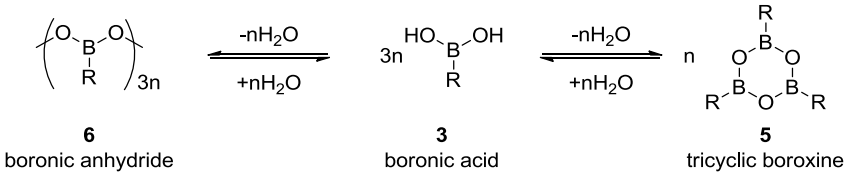
Boronic acids (**3**) are trivalent organoboron compounds containing one C-B bond and two hydroxyl groups in a trigonal planar geometry. They typically exist as white crystalline solids that are easy to handle. Although they are generally chemically stable in air at room temperature, slow atmospheric oxidation of boronic acids eventually affords boric acid (**4**), which is highly toxic to mammals and carries the risk of infertility to humans (***Scheme 2***).[6,7]



Scheme 2. Slow decomposition of boronic acids under aerobic conditions.

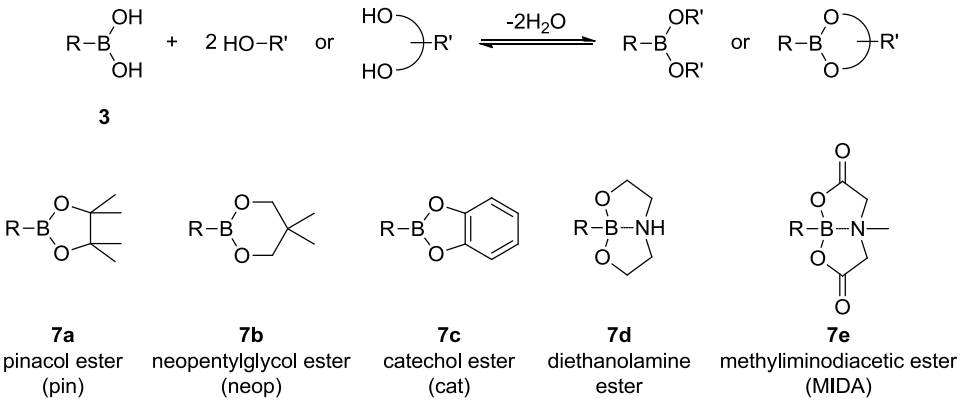
Special precautions are required for the less stable alkyl-substituted and some heteroaromatic variants.[8] Despite recent evidence citing mutagenic properties,[9,10] boronic acids is still widely considered as attractive intermediates in synthetic organic chemistry.

Boronic acids have a tendency to form a cyclic trimeric boroxine (**5**) and higher oligomeric anhydrides (**6**) under dry conditions can complicate analysis, quantification, purification and characterisation (***Scheme 3***).



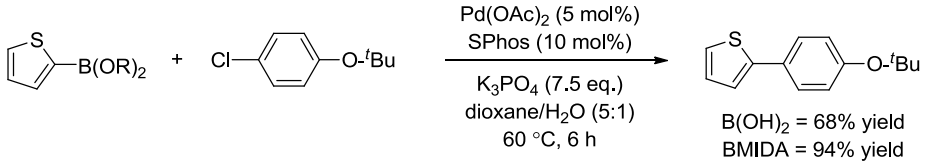
Scheme 3. Reversible condensation of boronic acids.

Although the average C-B bond is relatively strong (323 kJ mol^{-1} *versus* 358 kJ mol^{-1} for a C-C bond)[11] all boronic acid derivatives can undergo protolytic deboronation under a variety of acid, base, thermal and/or metal induced conditions.[12-19] The tendency of boronic acids to form anhydrides or undergo protolytic deboronation has led to the use of more stable derivatives as surrogates. Of these, the most common derivatives are the esters **7a-e** as they are readily formed by simple condensation reactions of the boronic acid with the corresponding alcohol (***Scheme 4***).



Scheme 4. Commonly used boronate esters.

Whilst reducing the deleterious side reactions, the ester moieties can provide novel reactivity profiles. For example, recent work by Burke has shown that the slow hydrolysis of MIDA (methyliminodiacetic) boronate esters to the boronic acids in the presence of K_3PO_4 can minimise protodeboronation in Suzuki-Miyaura cross-coupling reactions (***Scheme 5***).[8]



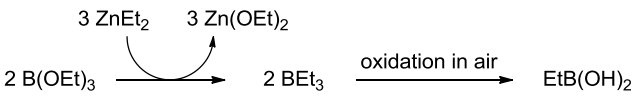
Scheme 5. MIDA boronate ester *versus* boronic acid in a Suzuki-Miyaura cross-coupling reaction.

1.3 Preparation Methods

Aryl, alkyl and alkenyl boronic acids can be synthesised in a variety of ways. This includes the classical reaction of an organometallic reagent with a suitable boron electrophile and the increasingly popular transition-metal mediated C-H activation of substrates. Despite this, the challenge remains to develop a robust, efficient and economical method amenable for the production of all types and structures of boronic acids. A comprehensive review on the syntheses of boronic acids falls outside of the scope of this thesis. The following section will serve only to give an overview of this subject matter, highlighting the benefits and drawbacks of the main synthetic methods that have been developed to date.

1.3.1 *Via* Organometallic Reagents or Intermediates

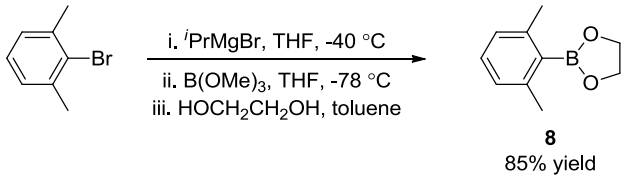
As shown by Frankland in 1860, trapping of an organometallic reagent with a suitable boron electrophile was the earliest synthetic methodology developed for the preparation of boronic acids (***Scheme 6***).[1-3]



Scheme 6. First preparation of a boronic acid.

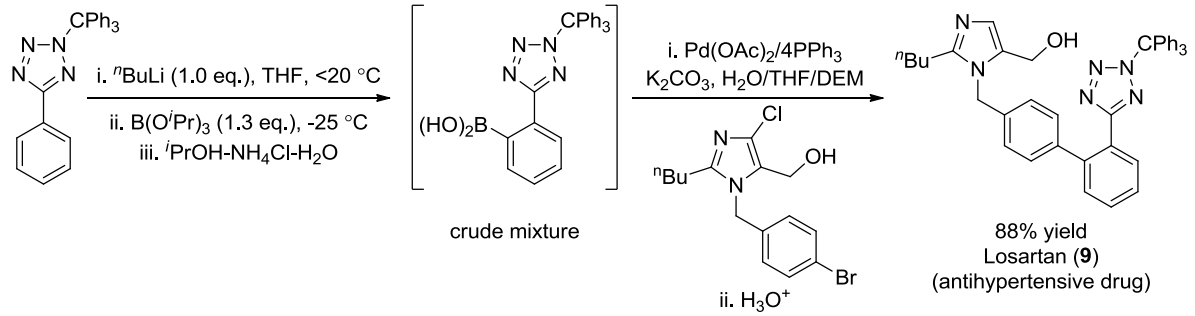
Subsequent development of this methodology has led to the use of simple Grignard and organolithium reagents in combination with a suitable trialkylborate electrophile. These reactions, which typically proceed through an initial metal-halogen exchange, even enable

access to sterically hindered arylboronic acids, for example 2-(2,6-dimethylphenyl)-1,3,2-dioxaborolane (**8**) (***Scheme 7***).[20]



Scheme 7. Synthesis of a sterically hindered arylboronate ester *via* a Grignard intermediate.

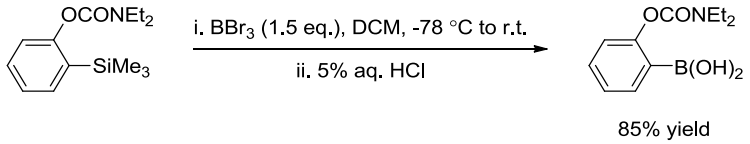
One useful extension of this methodology involves directed C-H metalation of arenes containing *ortho*-directing functional groups such as amines, ethers, anilides, esters, amides and carbamates. Crude boronic acid mixtures obtained from *ortho*-lithiation can often be used directly in Suzuki-Miyaura cross-coupling reactions, for example, in the synthesis of Losartan (**9**) (***Scheme 8***).[21]



Scheme 8. Synthesis of Losartan.

Transmetalation of a boron electrophile with other organometals have also been reported. Of these reactions, the use of zirconecene intermediates[22] and aryl cadmium are less effective,[23] whilst diaryl mercury is generally avoided due to its toxicity.[24,25] Aryl silanes and aryl stannanes on the other hand, are less toxic and undergo smooth transmetalation with

hard boron halides (***Scheme 9***).[26] This is because the transmetalation process is thermodynamically driven by the greater stability of the B-C and Si(Sn)-X bonds formed in the products relative to the corresponding B-X and Si(Sn)-C bonds in the starting reagents.[27]

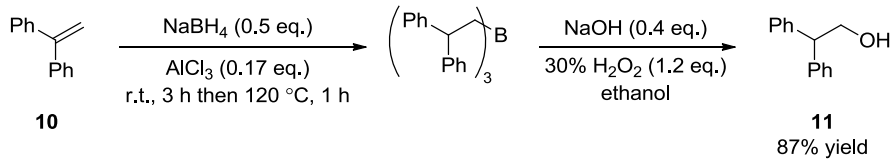


Scheme 9. *Ipso*-borylation of an aryl silane.

Although these methods do form aryl, alkyl and alkenyl boronic acids, the requirement of either hard or highly toxic organometals leads to health and safety issues and a limited range of structural variety and functional groups in the final products. Moreover, the low temperature and anhydrous conditions required to minimise the formation of a borinate side-product arising from double alkylation, is an inconvenient practical hindrance. Consequently, many alternative strategies have been explored.[28,29] Among these, the key methodologies are summarised in the following sections.

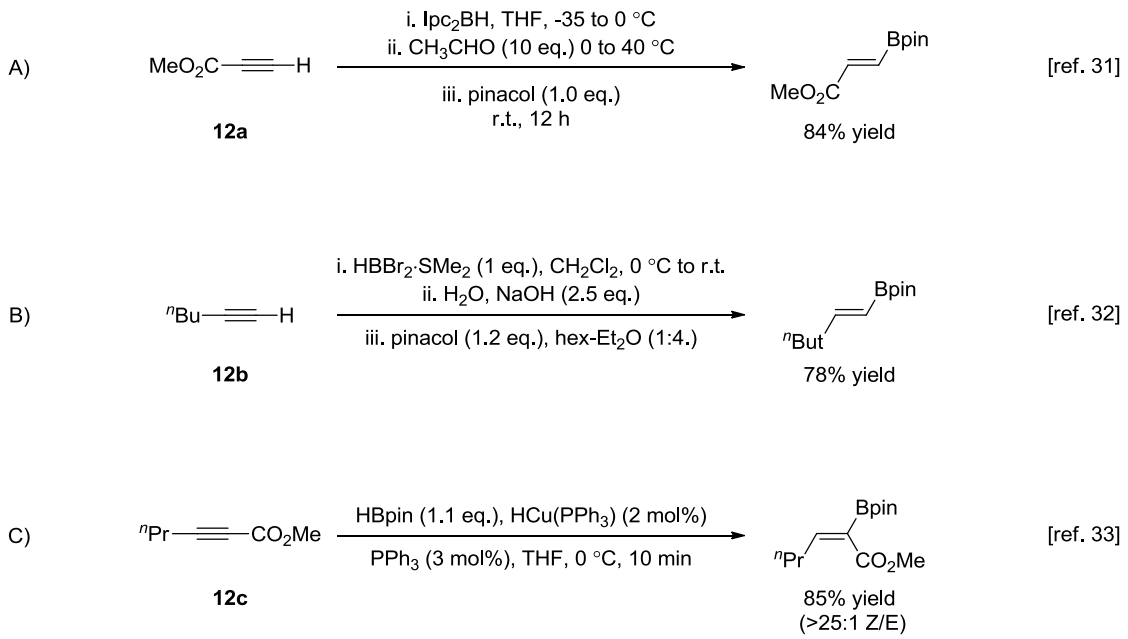
1.3.2 Hydroboration of Unsaturated C-C Bonds

Hydroboration as a route to trialkylboranes was first developed by Brown and Subba Rao in 1956 through the treatment of simple alkenes such as ethene-1,1-diyldibenzene (**10**) with $NaBH_4$ in the presence of aluminium chloride. Subsequent oxidation affords the corresponding alcohol **11** *via* boronate ester and trialkylborate intermediates (***Scheme 10***).[30]



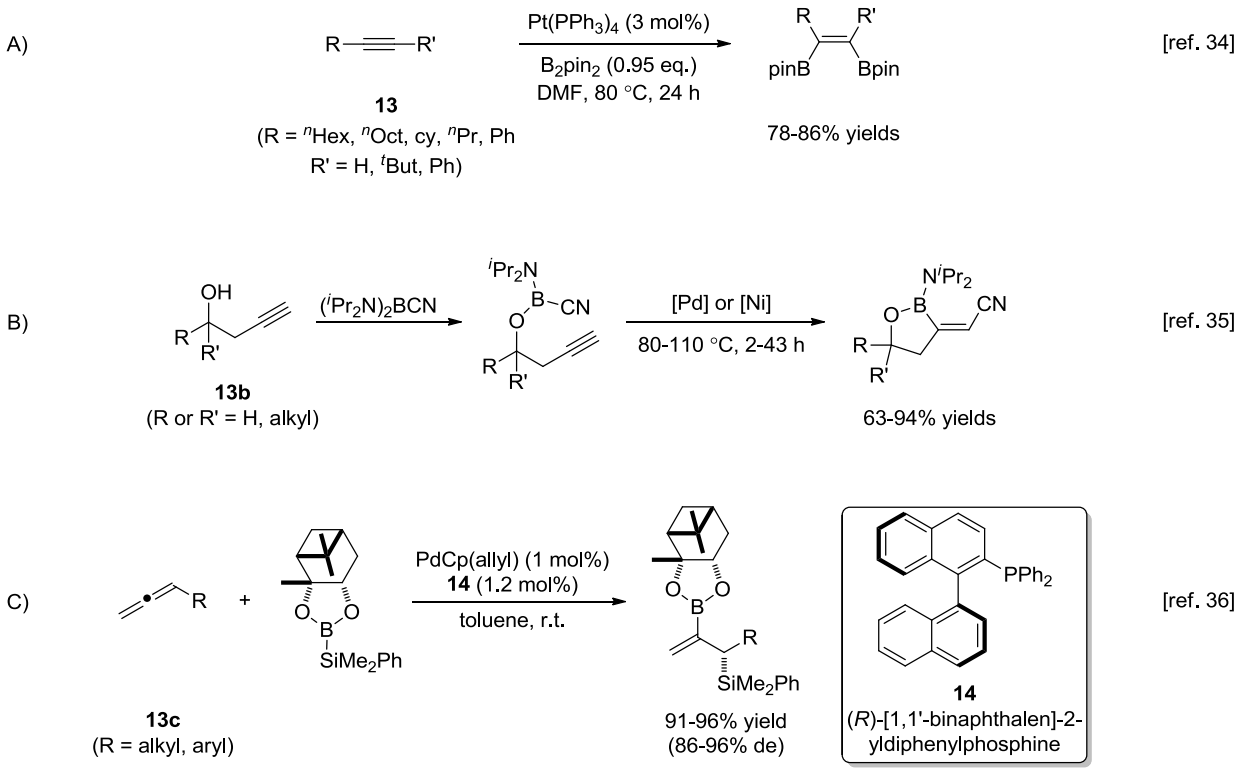
Scheme 10. Hydroboration of simple alkenes with sodium borohydride.

Subsequently, the related borane (BH_3) has become a popular choice of boron electrophile for the synthesis of alcohols from olefins. Controlling this oxidation process to obtain the initially formed alkylboronic acids, however, is difficult. In the hydroboration of alkynes, the use of dialkylboranes such as Ipc_2BH to give dialkyl alkenylborane intermediate has allowed for the selective oxidation of C(sp^3)-B over C(sp^2)-B bonds, affording the desired boronic acid (***Scheme 11A***).[31] Selective hydrolysis following hydroboration with dihaloboranes has also been reported (***Scheme 11B***).[32] With the emergence of dialkoxyboranes and diaryloxyboranes as stable and commercially available reagents, both alkyl and alkenylboronate esters can now be synthesised directly through the hydroboration of alkenes and alkynes (***Scheme 11C***).[33]



Scheme 11. Terminal *versus* internal alkyne hydroboration.

Hydroboration generally requires heating or the presence of a transition metal and typically proceeds with an anti-Markovnikov addition of a B-H bond. This strategy is thus particularly suited for the synthesis of terminal alkyl and alkenyl boronic acids. The ability to select between the two ends of unsymmetrical internal double or triple bonds and achieve regioselective addition across an internal double bond, however, remains a challenge. While hydroboration of terminal and internal alkynes is selective towards *cis*-addition of a B-H bond, the opposite trans-addition has yet to be achieved. This is best exemplified by the hydroboration of two representative propiolate derivatives **12a** and **12c**. The related diborylation (***Scheme 12A***),[34] cyanoboration (***Scheme 12B***)[35] and silaboration (***Scheme 12C***)[36] of alkynes **13a-c** have also been reported to give products with an extra functional group handle.

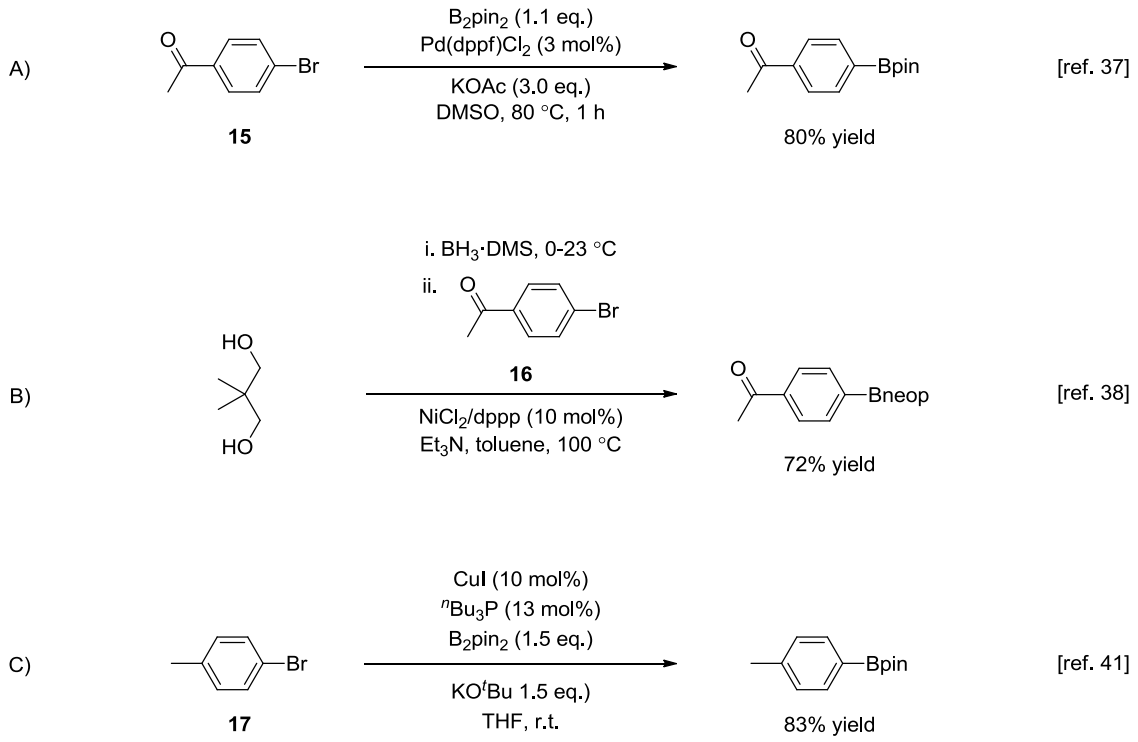


Scheme 12. Examples of diboronylation, cyanoboration and silaboration of alkenes.

1.3.3 Metal-Catalysed Coupling of Aryl Halides

Recent development of palladium-catalysed borylation of aryl halides and triflates in the presence of a diboronyl reagent provides access to a wide range of structurally diverse aryl boronic acids compared to the methods that require organometallic reagents. Borylation of ketone-containing 1-(4-bromophenyl)ethanone (**15**) for example, is possible using a palladium catalyst (***Scheme 13A***).[37] The related nickel-catalysed borylation of aryl halides such as **16** to give arylBneop have also been reported (***Scheme 13B***).[38] These reactions were later successfully extended to aryl mesylates and tosylates.[39] More recently, Zhu and Ma have developed a copper-catalysed variation of these borylation reactions using copper(I)

iodide in the presence of sodium hydride and pinacolborane.[40] Although this methodology was initially limited to aryl iodides, Marder and co-workers later showed that by employing an alkoxide base and a phosphine ligand among other changes, these reactions can be further extended to the bromides, for example **17** (***Scheme 13C***).[41]

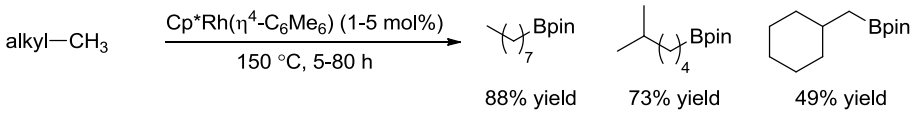


Scheme 13. Examples of Pd, Ni and Cu-catalysed C-X borylation.

These methodologies provide a simple and efficient route to aryl and alkenyl boronic acids. They are however, less suited to alkylboronic acids owing to the notoriously slow oxidative addition of C(sp^3)-X bond with palladium and the relatively fast β-hydride elimination of the alkyl-Pd-X species over the desired transmetalation with a boron electrophile. For these reasons, other metals such as nickel and copper have been explored and will be discussed in more detail in Chapter 5.

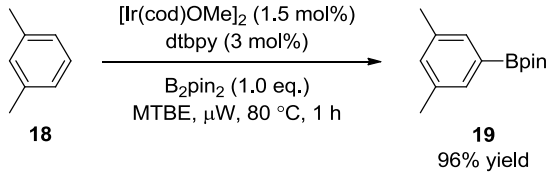
1.3.4 C-H Activation

More recently, there has been a great deal of focus on C-H bond activation using transition metals (*e.g.* Rh and Ir), circumventing the need for prefunctionalised reagents. While both thermal and photolytic conditions have been reported, developing a catalytic method with the ability to differentiate and activate particular C-H bonds remains a challenge. Despite the weaker bond-strengths of secondary and tertiary C-H bonds relative to primary C-H bonds,[42] transition-metal catalysed C-H activation of simple alkanes typically proceed with high selectivity in favour of the less sterically hindered terminal carbon (***Scheme 14***).[43] Borylation of a specific internal C-H bond would be more synthetically useful. However, this has yet to be achieved.



Scheme 14. Borylation of a terminal alkyl group through rhodium-catalysed C-H activation.

Such steric effects however, can be beneficially exploited in aromatic systems. For example, suitably substituted arenes can be used to direct activation, through sterics in iridium-catalysed aromatic C-H borylation employing bipyridyl ligands (see Chapter 2). In these reactions the addition of the boryl group avoids sterically hindered positions such as C-H bonds *ortho* to substituents or ring junctions in fused-ring systems. The borylation of *m*-xylene (**18**) for example, gives a single product **19** where the boryl group is installed at the only sterically accessible 5-position (***Scheme 15***).[44]

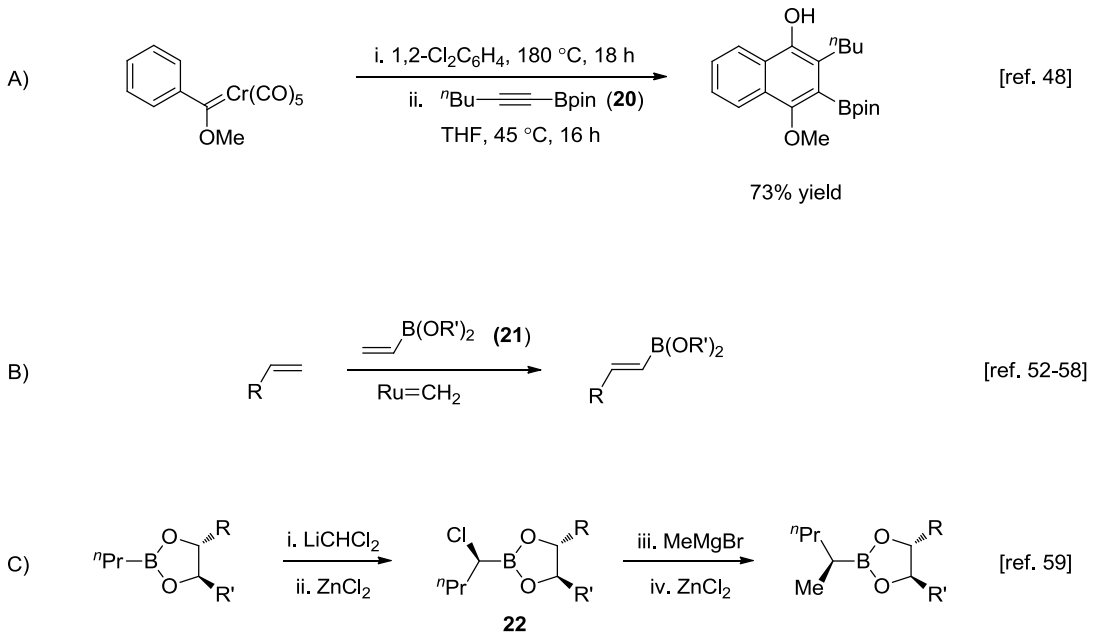


Scheme 15. Ir-bipyridyl C-H borylation of *m*-xylene.

However, when more than one C-H bond is accessible, a mixture of regioisomers and/or multiply borylated products are possible, and represents an issue which remains to be resolved. This transformation is central to this thesis and is discussed in greater details in Chapter 2.

1.3.5 Elaboration of Pre-formed Boronate Esters

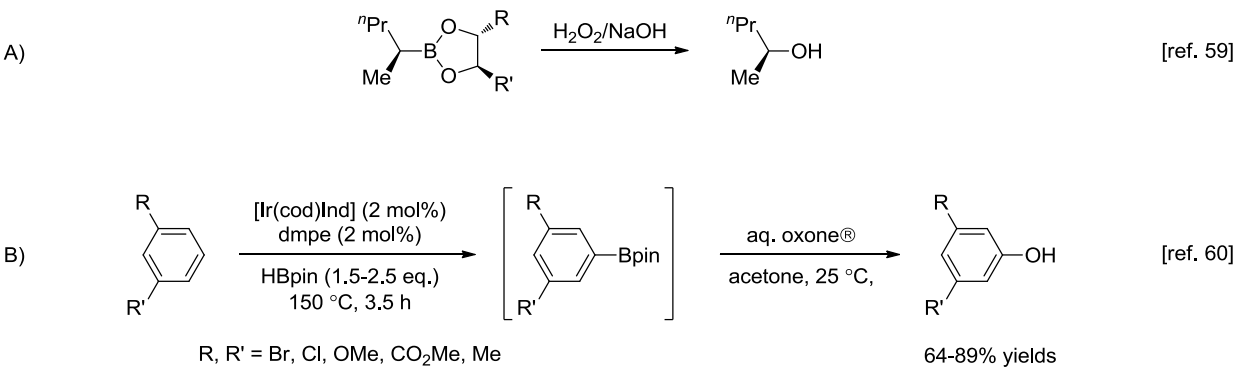
There are other methods for the preparation of boronic acids, but a comprehensive review of these synthetic routes is beyond the scope of this thesis. It is worth noting, however, that one useful approach involves the elaboration of preformed boronate esters (***Scheme 16***). These examples include the cycloadditions of alkynylboronates such as **20** followed by aromatisation for the preparation of aryl boronic acids (***Scheme 16A***),[45-51] and the use of simple alkenyl boronate esters **21** in alkene metathesis for the preparation of extended alkenyl boronic acids (***Scheme 16B***).[52-58] A more popular example is the Matteson's homologation strategy, which utilises an iteration of stereospecific displacement of halide from an α-haloalkylboronate ester **22** and a reaction with (dihalomethyl)lithium to install an additional stereocentre (***Scheme 16C***).[59] Such methodology is ideal for the preparation of chiral aliphatic boronate esters with multiple stereocentres.



Scheme 16. Elaboration of preformed boronate esters.

1.4 Reactions of Boronic Acids and Boronate Esters

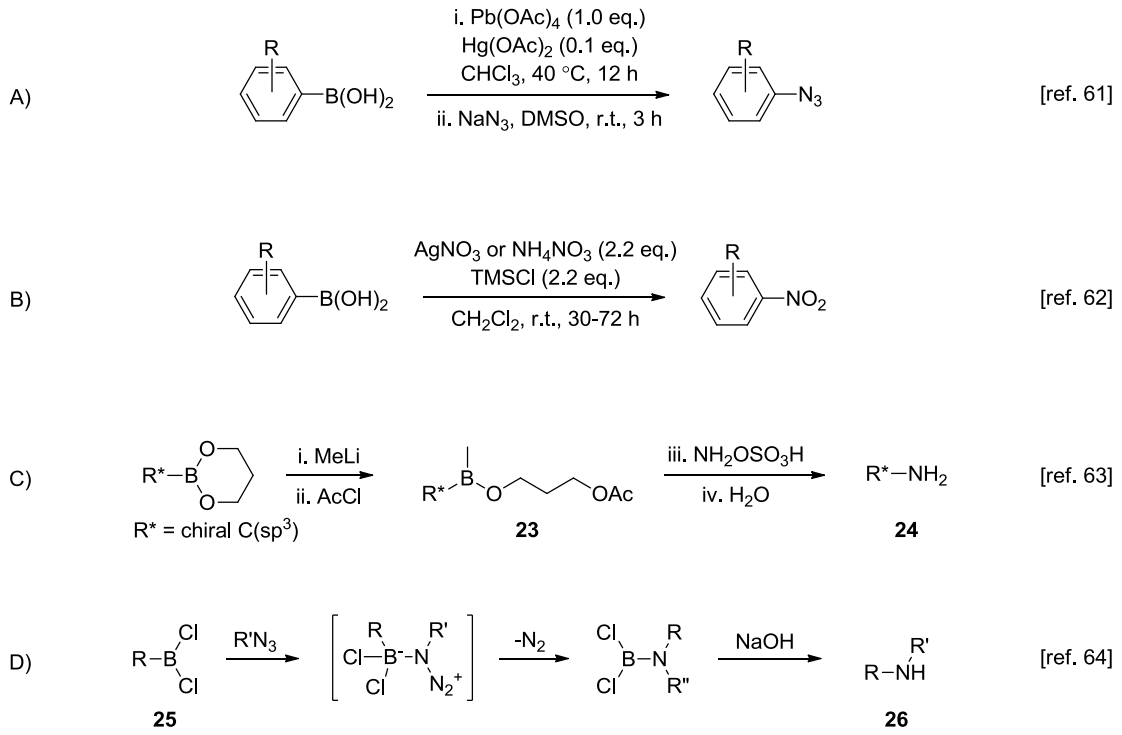
Boronic acids are ideal as intermediates, cross-coupling partners and precursors for a wide range of functional groups. For example, oxidation of boronic acid derivatives using an aqueous mixture of hydrogen peroxide and a hydroxide base is particularly a popular method of preparing alcohols. This oxidative replacement of boron proceeds with retention of configuration, which is ideal for the preparation of chiral aliphatic alcohols following either asymmetric hydroboration of olefins or as a conclusion of Matteson's homologation strategy (for example, ***Scheme 17A***). Oxidation of arylboronate esters to phenols has also found wide use. For example, in the preparation of 3,5-disubstituted phenols when combined with an iridium-catalysed aromatic C-H borylation of 1,3-disubstituted benzenes (***Scheme 17B***).[60]



Scheme 17. Alcohols from organoboronate esters.

Ipso-azidation (***Scheme 18A***)[61] and *ipso*–nitration (***Scheme 18B***)[62] of arylboronic acids are also straightforward. However, *ipso*-amination to primary and secondary alkylamines is more difficult and requires the intermediacy of more electrophilic boron substrates.

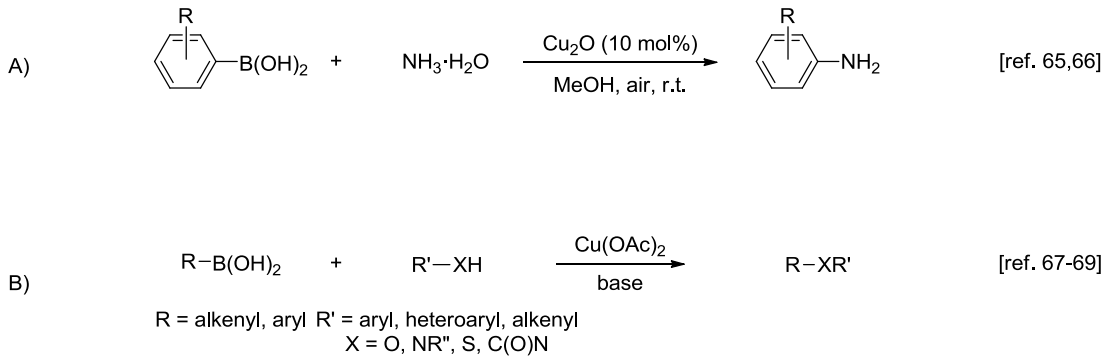
Optically pure primary amines (*e.g.* **24**) for example, can be generated from borinic esters (**23**) (***Scheme 18C***)[63] and optically pure secondary amines (**26**) from dichloroboranes (**25**) (***Scheme 18D***).[64]



Scheme 18. *Ipso*-azidation, -nitration and -amination of boronic acid derivatives.

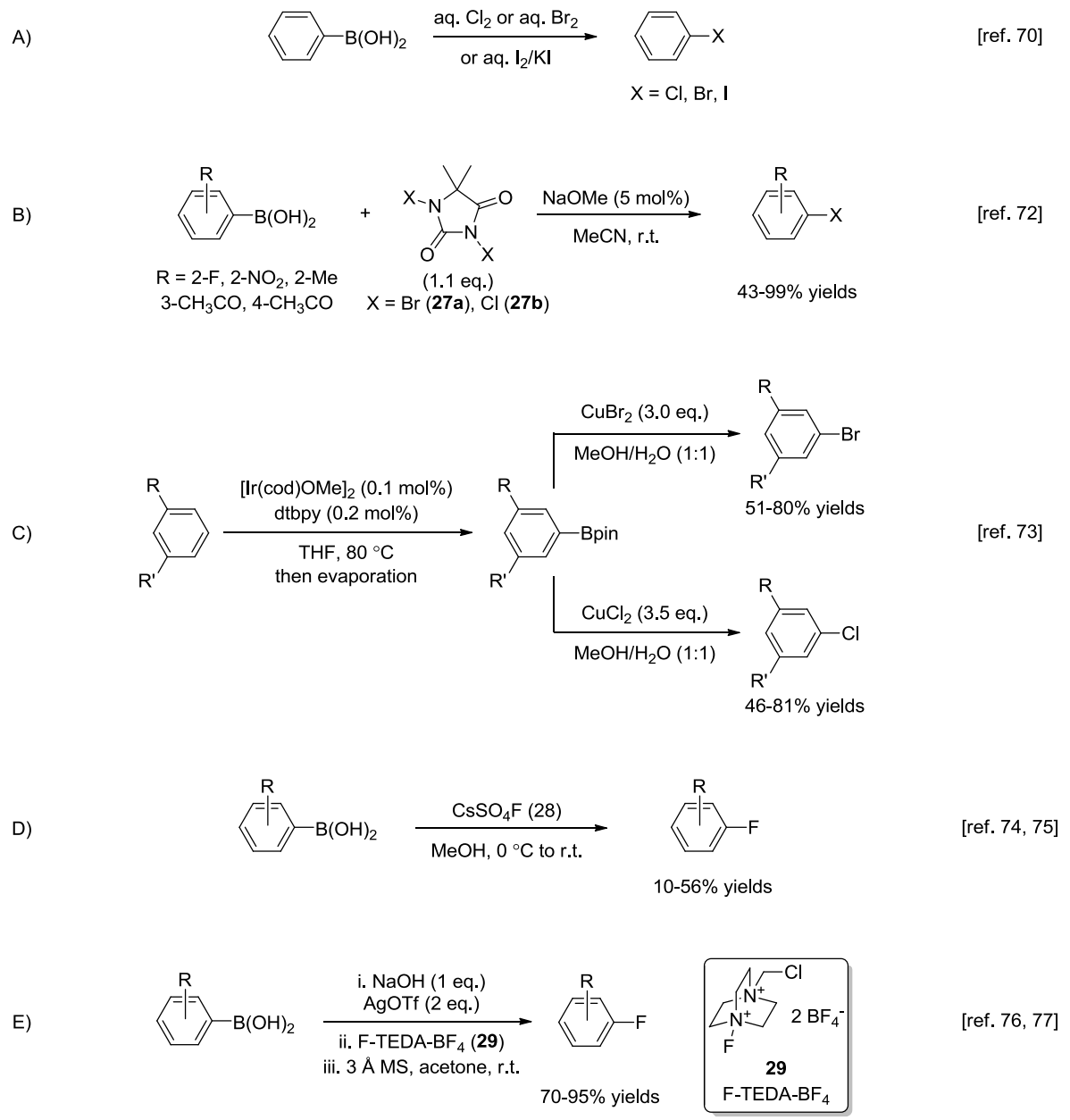
In contrast, aniline derivatives can be easily prepared from arylboronic acids using a copper(I) oxide catalyst and aqueous ammonia (***Scheme 19A***).[65,66] *N*-arylation as a route to diarylamines is also possible using a different copper salt such as copper(II) diacetate (***Scheme 19B***).[67-69] A wide variety of other C-heteroatom bond-forming reactions are also possible under these conditions to give ethers, thioethers and amides. A wide variety of conditions employing a combination of different copper catalyst precursors, bases and

additives have since been developed in the effort to facilitate this type of transformation with greater efficiency.



Scheme 19. Selected copper-promoted C-heteroatom bond-forming processes.

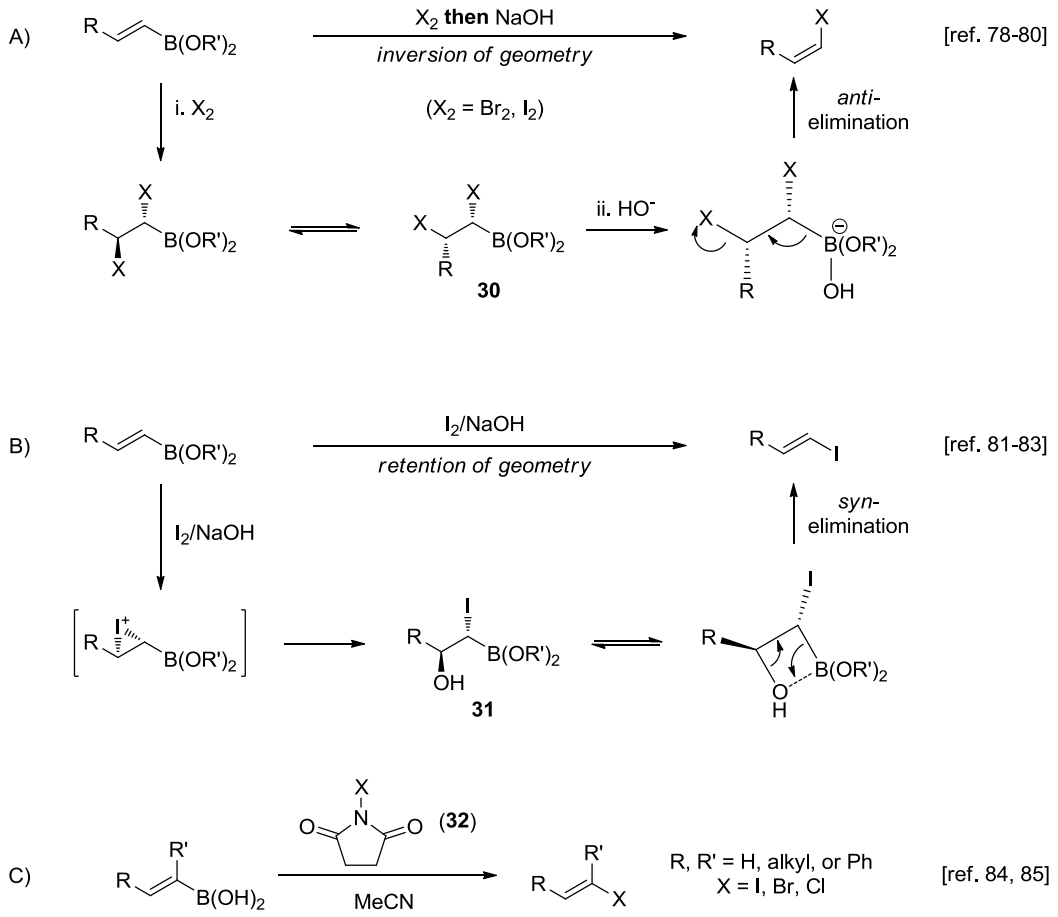
Halodeboronation of arylboronic acids can be achieved using aqueous chlorine, aqueous bromine and aqueous iodine/KI mixtures to give the corresponding aryl halides (***Scheme 20A***).[70] Whilst improved yields can be obtained with *N*-bromo and *N*-iodosuccinimides in acetonitrile under reflux,[71] a combination of 1,3-dibromo-5,5-dimethyldantoin (**27a**, DBDMH) or the chloride equivalent (DCDMH, **27b**), with sodium methoxide, has been found to be more efficient (***Scheme 20B***).[72] A more contemporary method employs cuprous chloride or bromide, which can be used in combination with iridium-catalysed aromatic C-H borylation to generate the corresponding 3,5-disubstituted aryl halides (***Scheme 20C***).[73] Fluorodeboronation of arylboronic acids is more challenging and can be achieved with modest yield by treatment with cesium fluoroxysulfate (**28**) in methanol (***Scheme 20D***).[74,75] More recently, stepwise Pd(II)- and Ag(I)-promoted methods have been developed to give aryl fluorides in good yields (***Scheme 20E***).[76,77]



Scheme 20. Halodeboronation of aryl boronic acid derivatives.

Bromo- and iododeboronation of alkenyl boronic acids can be accomplished using sequential treatment of Br_2 or I_2 and sodium hydroxide in one-pot. These reactions are widely believed to proceed *via* an initial dihalogenation of the double bond, which upon addition of the hydroxide base, leads to an anti-elimination of a halide and $(OH)B(OR')_2$ from **30** to give the corresponding alkenyl halide with inverted olefin geometry (***Scheme 21A***).[78-80] Simultaneous

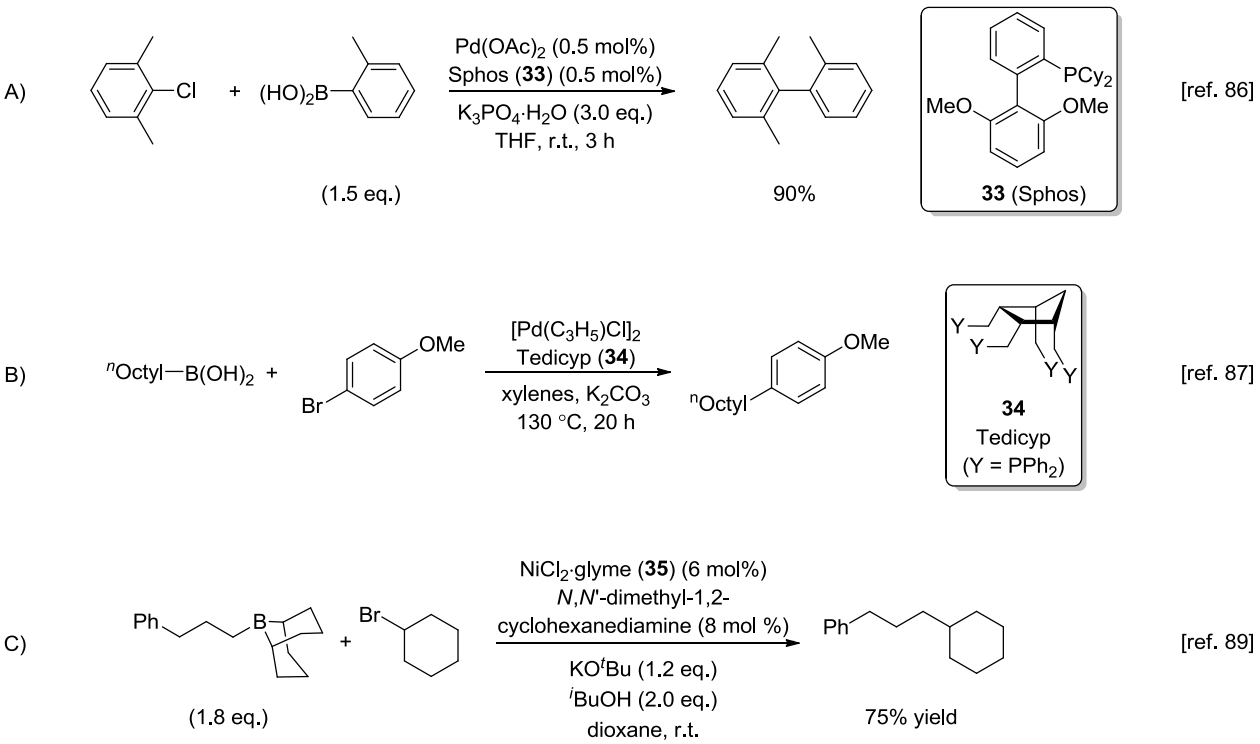
addition of I_2 and sodium hydroxide, however, gives alkenyl iodide with retention of geometry possibly due to *syn* elimination of $HOB(OR')_2$ from an iodohydrin intermediate **31** (***Scheme 21B***).[81-83] Alternatively, retention of geometry can also be achieved using halosuccinimides **32** as reagents (***Scheme 21C***).[84,85]



Scheme 21. Halodeboronation of alkenyl boronic acids.

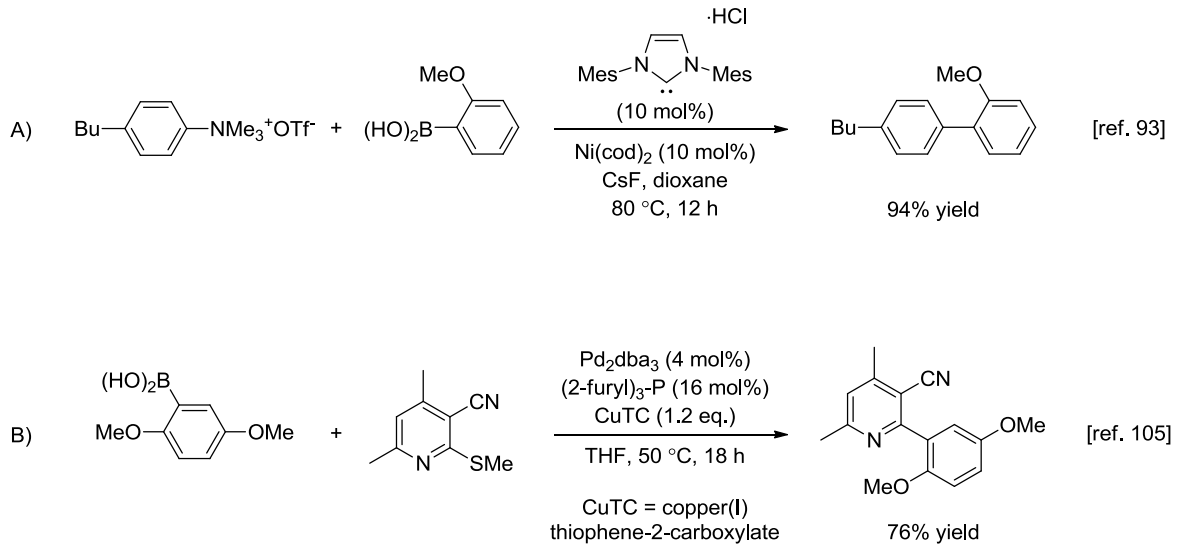
Boronic acids have found significant application in many C-C bond forming processes, notably palladium-catalysed Suzuki-Miyaura cross-coupling reactions with aryl halides (***Scheme 1***).[4,5] Extensive work on this palladium-catalysed methodology, particularly in the area of ligand design, has been central to the development of increasingly efficient

systems.[28] The cross-coupling of arylboronic acids with sterically hindered aryl chlorides can now be achieved in good yields using a combination of palladium(II) acetate, SPhos (**33**) ligand and aqueous K_3PO_4 under ambient temperature (***Scheme 22A***).[86] Even reactions involving an alkyl boronic acid can be carried out by using a small set of specific, particularly effective, ligands such as Tedicyp (**34**) (***Scheme 22B***).[87] Whilst examples of palladium-catalysed cross-coupling reactions of two sp^3 centres exist, these reactions are typically low-yielding owing to the notoriously slow oxidative addition of C(sp^3)-X bond to palladium and the thermodynamically more favourable β-hydride elimination of the resultant organopalladium over the desired transmetalation with the boronic acid derivative. This problem is exacerbated by the slower transmetalation of alkyl-boronic acids in comparison to arylboronic acids and slower reductive elimination of alkyl-alkyl when compared with an aryl-aryl unit.[88] One solution to this has been to use alternative metal catalysts. For example, Fu *et al*. have shown that nickel catalysts such as $NiCl_2$ (**35**) bound to a cyclohexyldiamine ligand are particularly effective (***Scheme 22C***).[89]



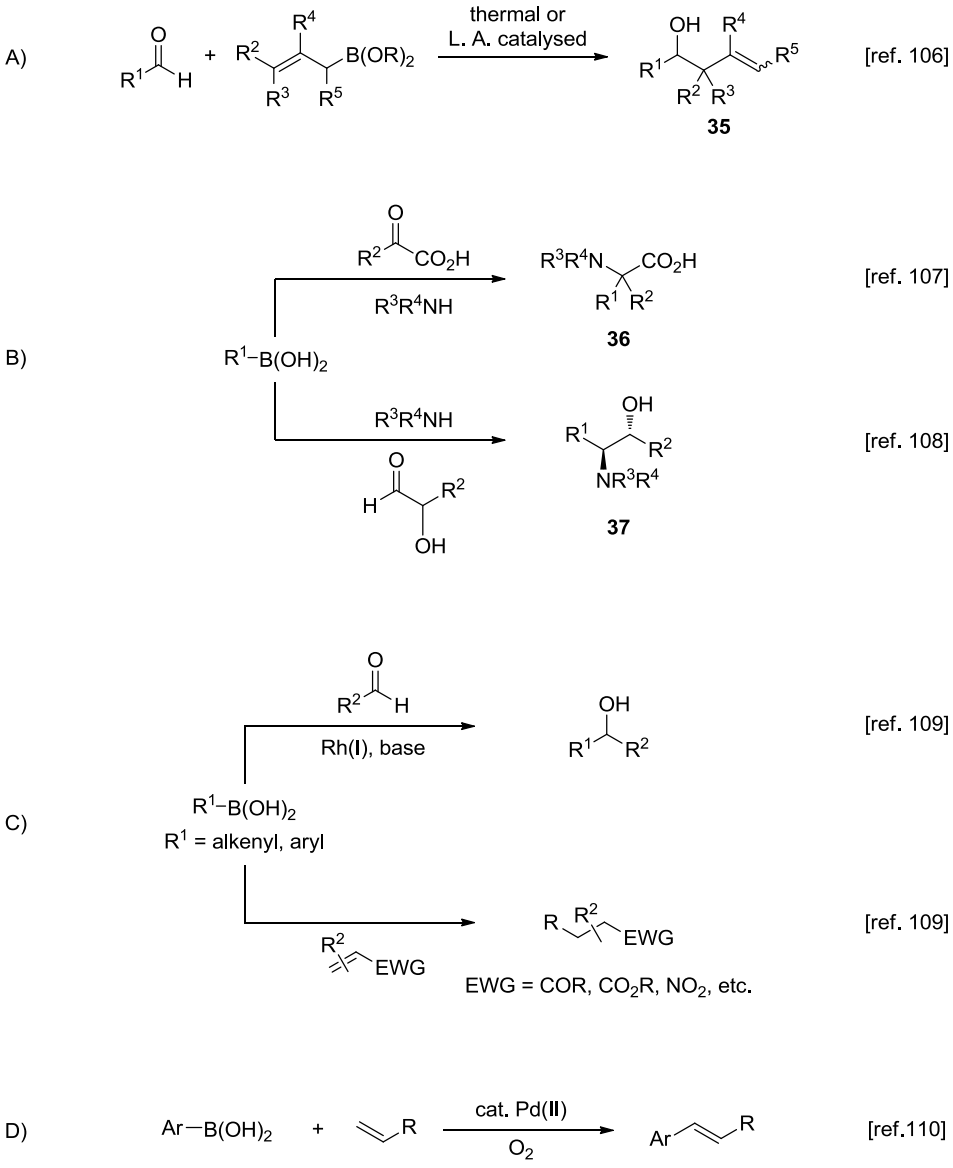
Scheme 22. Selected C-C bond-forming processes.

Whilst halides are the most common cross-coupling partners to arylboronic acids, other electrophiles have been successfully used such as aryltosylates,[90-92] arylammonium salts (***Scheme 23A***),[93] arylcarbamates and carbonates,[94-97] aryl methyl ethers,[98] arylsulfonium salts,[99] thioesters[100,101] and thioethers (***Scheme 23B***).[102-105]



Scheme 23. Alternative C-C bond cross-coupling partners to organohalides.

In addition to cross-coupling chemistry, there are many other important C-C bond-forming reactions of boronic acids. Addition of allylboronate esters to aldehydes is useful for the stereoselective synthesis of homoallylic secondary alcohols (*e.g*. **35**) (***Scheme 24A***).[106] Uncatalysed additions to imines and iminium ions, pioneered by Petasis, is another useful way of utilising boronic acids in stereoselective synthesis of useful small α-amino acids (**36**) or β-aminoalcohols (**37**) (***Scheme 24B***).[107,108] Rhodium-catalysed addition to carbonyls and a wide variety of olefins represents another useful potentially asymmetric C-C bond-formation (***Scheme 24C***).[109] Finally, oxidative addition of boronic acids to olefins provides a useful alternative to classical Heck chemistry (***Scheme 24D***).[110]



Scheme 24. Other examples of boronic acids in C-C bond-forming reactions.

1.5 Applications

The ability of boronic acids to form esters with alcohols is central to many of their applications beyond the use of these compounds as intermediates in synthetic organic chemistry. As catalysts and reaction promoters (through templation), boronic acids have been used in the hydrolysis of chloroalkanols,[111,112] etherification of chloroethanol,[101] amidation between amines and carboxylic acids,[113] aldol reactions,[114] Diels Alder reactions,[115] asymmetric ketone reduction[116,117] and many more. Other applications include their use as protecting groups for diols and diamines, and by extension, the immobilisation of these types of compounds on solid supports.[28] These are particularly useful strategies in carbohydrate chemistry and applications relating to the derivatisation, affinity purification and analysis of diols, sugars and glycosylated proteins have been described. [118-122] These include roles as sensors.

Away from synthetic chemistry, boronic acids have also found uses in medicine as antimicrobial agents, enzyme inhibitors,[123-125] drug carriers to facilitate membrane transport[126] and as boron carriers as part of neutron capture therapy for treatment of cancer.[127] Uses in related fields including protein labelling, bioconjugation and as probes in chemical biology have also been reported. More recently, boronic acids are being used to develop new materials and in self-assembly.[28]

1.6 References

[1] Frankland, E.; Duppa, B. F. *Justus Liebigs Annalen der Chemie* **1860**, *115*, 319.

[2] Frankland, E.; Duppa, B. *Proceedings of the Royal Society of London* **1859**, *10*, 568.

[3] Frankland, E. *J. Chem. Soc.* **1862**, *15*, 363.

[4] Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.

[5] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

[6] Ishii, Y.; Fujizuka, N.; Takahashi, T.; Shimizu, K.; Tuchida, A.; Yano, S.; Naruse, T.; Chishiro, T. *Clinical Toxicology* **1993**, *31*, 345.

[7] Restuccio, A.; Mortensen, M. E.; Kelley, M. T. *The American Journal of Emergency Medicine* **1992**, *10*, 545.

[8] Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

[9] O'Donovan, M. R.; Mee, C. D.; Fenner, S.; Teasdale, A.; Phillips, D. H. *Mutat. Res.* **2011**, *724*, 1.

[10] Ellis, P.; Kenyon, M.; Cheung, J.; Ackerman, J.; Caron, S.; Dobo, K. *Mutagenesis* **2010**, *25*, 657.

[11] Sana, M.; Leroy, G.; Wilante, C. *Organometallics* **1991**, *10*, 264.

[12] Snyder, H. R.; Wyman, F. W. *J. Am. Chem. Soc.* **1948**, *70*, 234.

[13] Kuivila, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2164.

[14] Kuivila, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2159.

[15] Snyder, H. R.; Kuck, J. A.; Johnson, J. R. *J. Am. Chem. Soc.* **1938**, *60*, 105.

[16] Johnson, J. R.; Van Campen, M. G.; Grummitt, O. *J. Am. Chem. Soc.* **1938**, *60*, 111.

[17] Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. *J. Org. Chem.* **1982**, *47*, 3808.

[18] Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Lee, H. D.; Negishi, E.; Katz, J. J. *J. Org. Chem.* **1986**, *51*, 5270.

[19] Matteson, D. S.; Peacock, K. *J. Org. Chem.* **1963**, *28*, 369.

[20] Wong, K. T.; Chien, Y. Y.; Liao, Y. L.; Lin, C. C.; Chou, M. Y.; Leung, M. K. *J. Org. Chem.* **2002**, *67*, 1041.

[21] Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C. H.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 6391.

[22] Cole, T. E.; Quintanilla, R.; Rodewald, S. *Organometallics* **1991**, *10*, 3777.

[23] Gilman, H.; Moore, L. O. *J. Am. Chem. Soc.* **1958**, *80*, 3609.

[24] Michaelis, A.; Becker, P. *Chem. Ber.* **1880**, *13*, 58.

[25] Michaelis, A.; Becker, P. *Chem. Ber.* **1882**, *15*, 180.

[26] Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093.

[27] Haubold, W.; Herdtle, J.; Gollinger, W.; Einholz, W. *J. Organomet. Chem.* **1986**, *315*, 1.

[28] Hall, D. G. *Boronic acids : preparation and applications in organic synthesis and medicine*; Wiley-VCH Verlag GmbH: Weinheim, 2005;

[29] Hall, D. *Boronic acids : volume 1 : preparation and applications in organic synthesis, medicine and materials*; Wiley-VCH: Weinheim, 2011;

[30] Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 5694.

[31] Martinezfresneda, P.; Vaultier, M. *Tetrahedron Lett.* **1989**, *30*, 2929.

[32] Zheng, B.; Srebnik, M. *J. Organomet. Chem.* **1994**, *474*, 49.

[33] Lipshutz, B. H.; Boskovic, Z. V.; Aue, D. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 10183.

[34] Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018.

[35] Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358.

[36] Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174.

[37] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

[38] Rosen, B. M.; Huang, C.; Percec, V. *Org. Lett.* **2008**, *10*, 2597.

[39] Wilson, D. A.; Wilson, C. J.; Rosen, B. M.; Percec, V. *Org. Lett.* **2008**, *10*, 4879.

[40] Zhu, W.; Ma, D. *Org. Lett.* **2005**, *8*, 261.

[41] Kleeberg, C.; Dang, L.; Lin, Z. Y.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350.

[42] Tedder, J. M. *Angew. Chem., Int. Ed.* **1982**, *21*, 401.

[43] Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.

[44] Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586.

[45] Hilt, G.; Bolze, P. *Synthesis* **2005**, 2091.

[46] Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860.

[47] Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 866.

[48] Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Org. Chem.* **2001**, *66*, 3525.

[49] Yamamoto, Y.; Ishii, J. I.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712.

[50] Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *Tetrahedron* **2005**, *61*, 11501.

[51] Auvinet, A. L.; Harrity, J. P. A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 3893.

[52] Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995.

[53] Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

[54] Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

[55] Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

[56] Njardarson, J. T.; Biswas, K.; Danishefsky, S. J. *J. Chem. Soc., Chem. Commun.* **2002**, 2759.

[57] Renaud, J.; Graf, C. D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101.

[58] Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272.

[59] Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.

[60] Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792.

[61] Huber, M. L.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 721.

[62] Salzbrunn, S.; Simon, J.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485.

[63] Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761.

[64] Brown, H. C.; Salunkhe, A. M.; Singaram, B. *J. Org. Chem.* **1991**, *56*, 1170.

[65] Rao, H. H.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 1114.

[66] Jiang, Z. Q.; Wu, Z. Q.; Wang, L. X.; Wu, D.; Zhou, X. G. *Can. J. Chem.* **2010**, *88*, 964.

[67] Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.

[68] Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.

[69] Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

[70] Ainley, A. D.; Challenger, F. *J. Chem. Soc.* **1930**, 2171.

[71] Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141.

[72] Szumigala, R. H.; Devine, P. N.; Gauthier, D. R.; Volante, R. P. *J. Org. Chem.* **2004**, *69*, 566.

[73] Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

[74] Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1992**, *48*, 8073.

[75] Clough, J. M.; Diorazio, L. J.; Widdowson, D. A. *Synlett* **1990**, 761.

[76] Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993.

[77] Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.

[78] Brown, H. C.; Hamaoka, T.; Ravindra.N *J. Am. Chem. Soc.* **1973**, *95*, 6456.

[79] Brown, H. C.; Bhat, N. G.; Rajagopalan, S. *Synthesis* **1986**, 480.

[80] Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6068.

[81] Brown, H. C.; Hamaoka, T.; Ravindra.N *J. Am. Chem. Soc.* **1973**, *95*, 5786.

[82] Brown, H. C.; Somayaji, V. *Synthesis* **1984**, 919.

[83] Brown, H. C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6075.

[84] Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567.

[85] Kunda, S. A.; Smith, T. L.; Hylarides, M. D.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26*, 279.

[86] Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

[87] Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *60*, 3813.

[88] Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

[89] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602.

[90] Nguyen, H. N.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

[91] Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447.

[92] Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058.

[93] Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

[94] Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750.

[95] Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422.

[96] Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748.

[97] Guan, B. T.; Wang, Y.; Li, B. J.; Yu, D. G.; Shi, Z. J. *J. Am. Chem. Soc.* **2008**, *130*, 14468.

[98] Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.

[99] Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

[100] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229.

[101] Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

[102] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91.

[103] Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

[104] Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983.

[105] Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, *5*, 4349.

[106] Otera, J. *Modern carbonyl chemistry*; Wiley-VCH: Weinheim; New York, 2000;

[107] Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

[108] Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.

[109] Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

[110] Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231.

[111] Letsinger, R. L.; Dandegao, S.; Morrison, J. D.; Vullo, W. J. *J. Am. Chem. Soc.* **1963**, *85*, 2223.

[112] Letsinger, R. L.; Morrison, J. D. *J. Am. Chem. Soc.* **1963**, *85*, 2227.

[113] Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196.

[114] Arnold, K.; Batsanov, A. S.; Davies, B.; Grosjean, C.; Schutz, T.; Whiting, A.; Zawatzky, K. *J. Chem. Soc., Chem. Commun.* **2008**, 3879.

[115] Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171.

[116] Molander, G. A.; Bobbitt, K. L.; Murray, C. K. *J. Am. Chem. Soc.* **1992**, *114*, 2759.

[117] Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 7517.

[118] Gray, C. W.; Houston, T. A. *J. Org. Chem.* **2002**, *67*, 5426.

[119] Zhao, J. Z.; Fyles, T. M.; James, T. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 3461.

[120] James, T. D.; Sandanayake, K.; Shinkai, S. *Angew. Chem., Int. Ed.* **1996**, *35*, 1910.

[121] James, T. D.; Shinkai, S. In *Host-Guest Chemistry: Mimetic Approaches to Study Carbohydrate Recognition*; Penades, S., Ed.; Springer-Verlag Berlin: Berlin, 2002; Vol. 218; p 159-200.

[122] Wang, W.; Gao, X. M.; Wang, B. H. *Curr. Org. Chem.* **2002**, *6*, 1285.

[123] Yang, W. Q.; Gao, X. M.; Wang, B. H. *Med. Res. Rev.* **2003**, *23*, 346.

[124] Akparov, V. K.; Stepanov, V. M. *J. Chromatogr.* **1978**, *155*, 329.

[125] Cartwright, S. J.; Waley, S. G. *Biochem. J.* **1984**, *221*, 505.

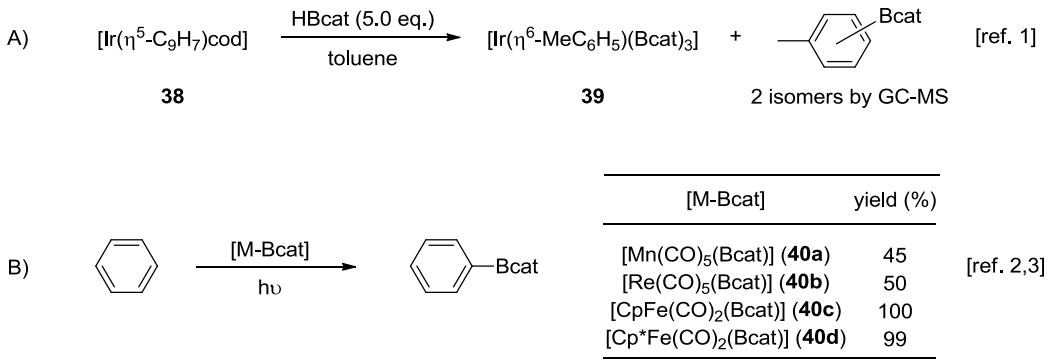
[126] Gokel, G. W.; International Union of, P.; Applied, C. *Advances in supramolecular chemistry. Volume 5, 1999*; Jai Press: Stamford, Connecticut, 1999;

[127] Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F. G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.

Chapter 2 - Iridium-Catalysed Aromatic C-H Borylation of Mono- and Unsymmetrical 1,2-Disubstituted Benzenes: Insights Into Steric and Electronic Effects on Selectivity

2.1 Introduction to Iridium-Catalysed Aromatic C-H Borylation

Selective activation of ubiquitous C-H bonds is a synthetically useful way of converting unreactive hydrocarbons into desirable functionalised molecules. Of these reactions, aromatic C-H borylation is particularly useful as the resultant arylboron compounds can be used in a wide variety of chemical transformations (see Chapter 1). The first reported observation of aromatic C-H borylation was the substoichiometric formation of a borylated toluene solvent in the preparation of a trisboryl iridium complex **38** (***Scheme 1A***).[1] Shortly after, Hartwig and co-workers reported stoichiometric borylation of arenes using defined metal-boryl complexes $[Mn(CO)_5(Bcat)]$ (**40a**), $[Re(CO)_5(Bcat)]$ (**40b**), $[CpFe(CO)_2(Bcat)]$ (**40c**), and $[Cp^*Fe(CO)_2(Bcat)]$ (**40d**) under photolytic conditions (***Scheme 25B***).[2,3]



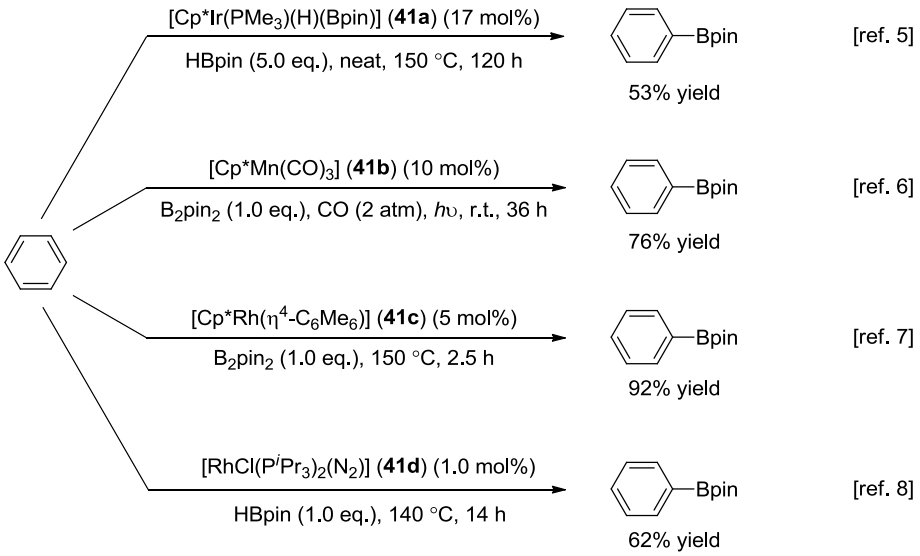
[M-Bcat]	yield (%)
$[Mn(CO)_5(Bcat)]$ (**40a**)	45
$[Re(CO)_5(Bcat)]$ (**40b**)	50
$[CpFe(CO)_2(Bcat)]$ (**40c**)	100
$[Cp^*Fe(CO)_2(Bcat)]$ (**40d**)	99

Scheme 25. Earliest reports on borylation of arenes through functionalisation of C-H bonds.

The following section gives a brief overview of how aromatic C-H borylation has evolved to become an efficient catalytic system. For a more comprehensive review of this process, see reference 4.[4]

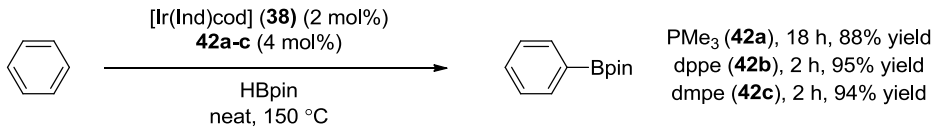
2.1.1 Catalytic Aromatic C-H Borylation

The earliest reports of catalytic aromatic C-H borylation involved the use of Cp*-Ir, -Mn and -Rh complexes (**41a-c**) and a rhodium complex [Rh(Cl)(N_2)(P^iPr_3)$_2$] (**41d**) (***Scheme 26***).[5-8] Of these, the rhodium system employing [Rh(Cl)(N_2)(P^iPr_3)$_2$] precursor (**41d**) showed a particularly high turnover number, although the preferential borylation of benzylic C-H bonds may represent a problem for selective aromatic borylation of substrates such as toluene.[8]



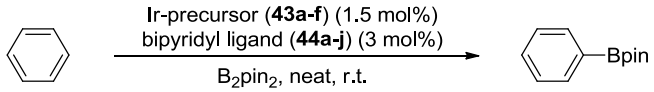
Scheme 26. First examples of catalytic aromatic C-H borylation.

Building on Marder's original report[1] and Hartwig's work on phosphine iridium(III) boryl hydride complex,[5] Smith and co-workers reported a remarkably efficient catalyst for the borylation of arenes using a combination of [Ir(cod)Ind] (**38**) and a phosphine ligand such as PMe_3 (**42a**), dmpe (**42b**) or dppe (**42c**) (***Scheme 27***).[9]



Scheme 27. Iridium-catalysed aromatic C-H borylation with phosphine ligands.

Concurrent with this paper,[9] Hartwig, Ishiyama, Miyaura and co-workers reported that bipyridine Ir(III) complexes were effective catalysts for arene C-H borylation under mild conditions.[10] A systematic screening of a range of iridium(I)-cyclooctadiene precursors (**43a-f**) with a range of symmetrical disubstituted 2,2'-bipyridyl ligands (**44a-j**) showed that alkoxo-iridium complexes, particularly $[Ir(cod)OMe]_2$ (**43f**), were especially effective (***Table 1***, entries 1-6).[11] A screening of steric effects in 2,2'-bipyridyl ligands revealed that the ability of the two pyridyl rings to adopt a co-planar geometry and to coordinate unhindered to the iridium-metal centre are crucial for high levels of conversion (***Table 1***, entries 6-10). The presence of electron-withdrawing groups also appeared to have detrimental effects (***Table 1***, entries 14-15 vs. 10-13). Consistent with these observations, 2,2'-bipyridines containing methyl, methoxy, *tert*-butyl or dimethylamine groups at the 4- and 4'-positions are particularly effective ligands (***Table 1***, entries 10-13). While these experiments were conducted using neat arenes, further studies showed that these reactions can also be carried out in non-polar non-coordinating solvents. The combination of $[Ir(cod)OMe]_2$ (**43f**) and dtbpy (**44h**) in hexane is particularly effective, due to solubility reasons, and has since become the standard protocol for aromatic C-H borylation of arenes.



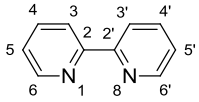
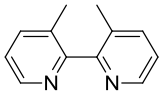
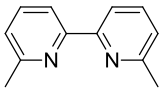
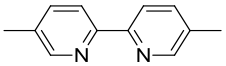
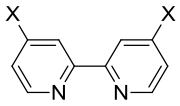
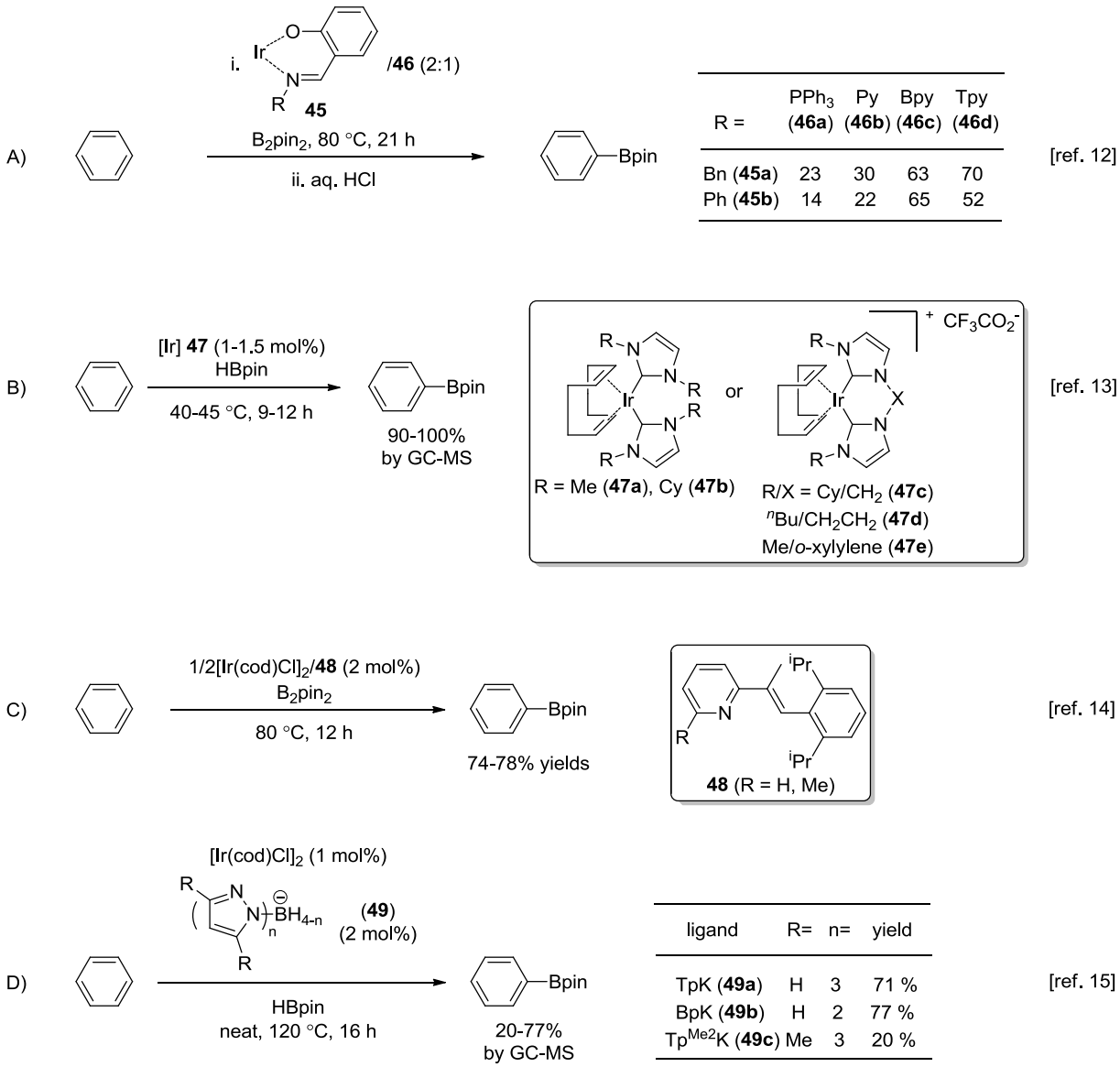
entry	Ir-precursor		bipyridyl ligand		time (h)	conv. (%)	GC-MS yield (%)
1	$[Ir(cod)Cl]_2$	**43a**			24	0	0
2	$[Ir(cod)_2]BF_4$	**43b**			24	3	0
3	$[Ir(cod)OAc]_2$	**43c**		(**44a**)	24	19	1
4	$[Ir(cod)OH]_2$	**43d**			4	100	88
5	$[Ir(cod)OPh]_2$	**43e**			4	100	84
6	$[Ir(cod)OMe]_2$	**43f**			4	100	90
7	$[Ir(cod)OMe]_2$	**43f**		(**44b**)	8	100	60
8	$[Ir(cod)OMe]_2$	**43f**		(**44c**)	24	27	0
9	$[Ir(cod)OMe]_2$	**43f**		(**44d**)	2	100	82
10	$[Ir(cod)OMe]_2$	**43f**	X = Me	(**44e**)	4	100	89
11	$[Ir(cod)OMe]_2$	**43f**	X = NMe_2	(**44f**)	2	100	89
12	$[Ir(cod)OMe]_2$	**43f**	 X = OMe	(**44g**)	4	100	90
13	$[Ir(cod)OMe]_2$	**43f**	X = ^{t}Bu	(**44h**)	4	100	83
14	$[Ir(cod)OMe]_2$	**43f**	X = Cl	(**44i**)	24	16	0
15	$[Ir(cod)OMe]_2$	**43f**	X = NO_2	(**44j**)	24	46	0

Table 1. Steric and electronic effects on a core bipyridine ligand.

Aromatic C-H borylation using iridium(I)-salicylaldiminato complexes (**45**),[12] biscarbene iridium complexes (**47a-c**)[13] and iridium complexes containing ligands such as 2,6-disubstituted pyridine (**48**),[14] and tris(pyrazolyl)borate (**49a-c**)[15] have all been reported (***Scheme 28***).

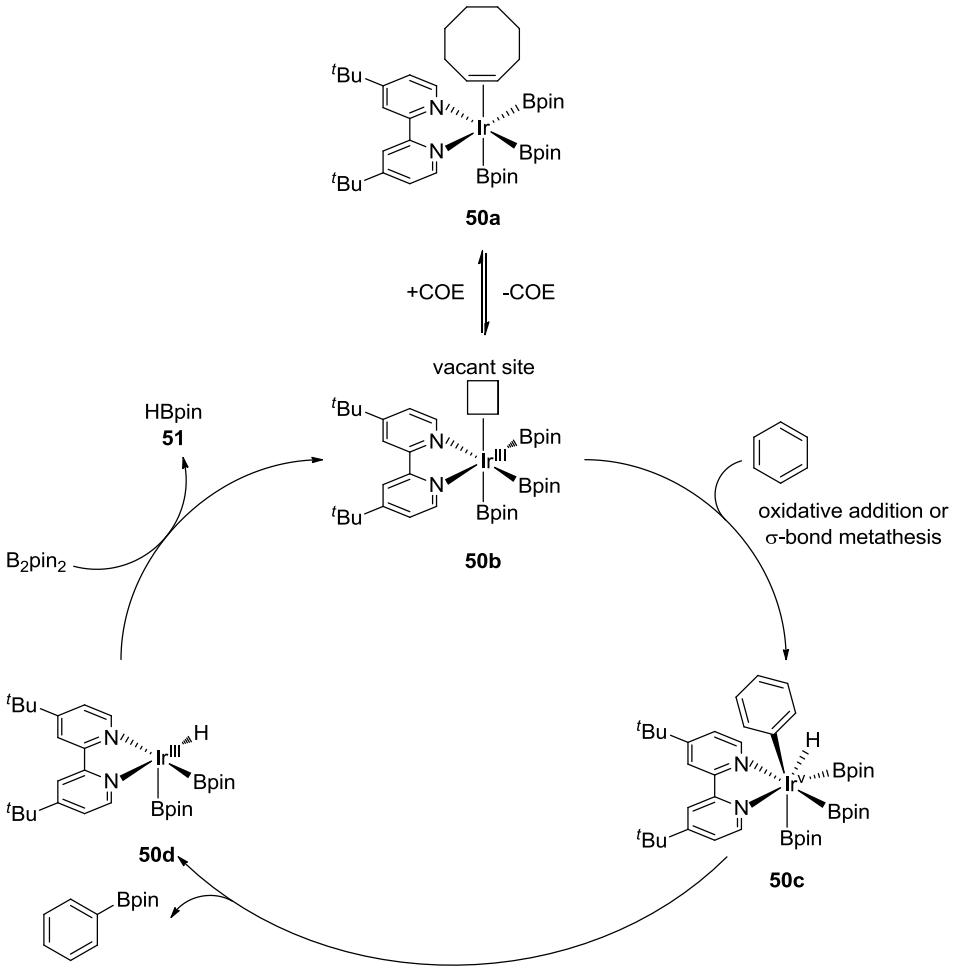


Scheme 28. Aromatic C-H borylation with a range of iridium(I) complexes.

2.1.2 Proposed Mechanism for Bipyridyl Ir(III) Complexes

Ishiyama, Hartwig, Miyaura and co-workers proposed that the aromatic C-H borylation of arenes using a catalyst generated from $[Ir(cod)X]_2$/dtbpy combination proceeds with an initial formation of a stable $[Ir(coe)(dtbpy)(Bpin)_3]$ complex (**50a**). Reversible dissociation of

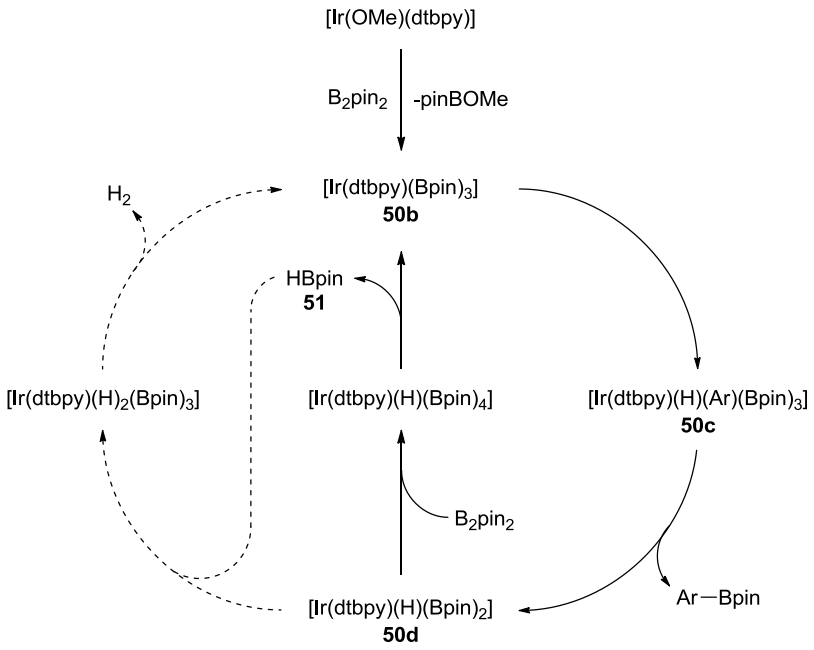
cyclooctene generates the 16-electron complex **50b** with a vacant site allowing oxidative addition of an aryl C-H bond. Reductive elimination of the arylBpin product from the resultant iridium(v) trisboryl complex **50c** gives an iridium(III) boryl complex **50d**. The active catalytic species **50b** is then regenerated through successive oxidative addition of B_2pin_2 and reductive elimination of HBpin (***Scheme 29***).[10,16]



Scheme 29. Proposed catalytic cycle for the borylation of benzene with $[Ir(cod)X]_2$/dtbpy.

The proposed formation of $[Ir(coe)(dtbpy)(Bpin)_3]$ (**50a**) as a key intermediate in the catalytic cycle is consistent with the reduction of cyclooctadiene to cyclooctene-d_2 observed in the

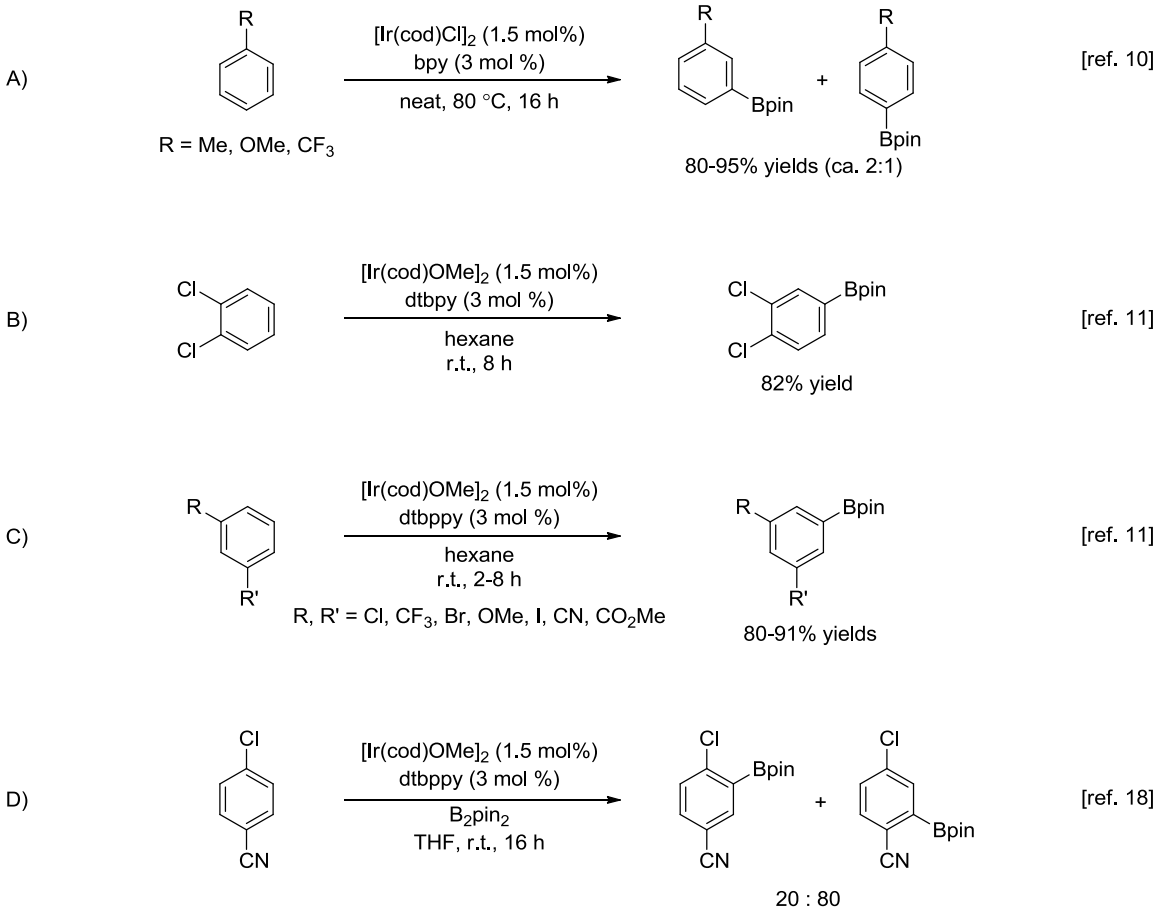
borylation of deuterated benzene. Moreover, the isolated trisboryl iridium complex reacts almost instantaneously in C_6D_6 at room temperature suggesting that **50a** is a competent reactive intermediate. The inhibitory effect of added coe supports the reversible dissociation of coe. A primary isotope effect observed in reactions involving the trisboryl complex **50a** with benzene and deuterated benzene suggests that the oxidative addition of an aryl C-H bond is the rate-limiting step. The formation of such a hindered iridium(V) complex **50c** is supported by computational studies carried out by Sakaki and co-workers and is attributed to the stabilisation effect of the electron-rich bipyridyl ligand.[17] This could account for the regioselectivity of these reactions, which is predominantly controlled by sterics (see Chapter 1). The same theoretical study also reported that an alternative mechanism involving σ-bond metathesis is less favourable. In addition, Sakaki and co-workers suggested that the mechanism could involve an additional catalytic cycle, which is much slower and involves the regeneration of [Ir(dtbpy)(Bpin)$_3$] (**50b**) through HBpin (**51**) generated from the first cycle (***Scheme 30***).



Scheme 30. Proposed regeneration of the active catalytic species through B_2pin_2 and HBpin.

2.1.3 Regioselectivity in Bipyridyl Ir(III)-Catalysed Borylation of Arenes

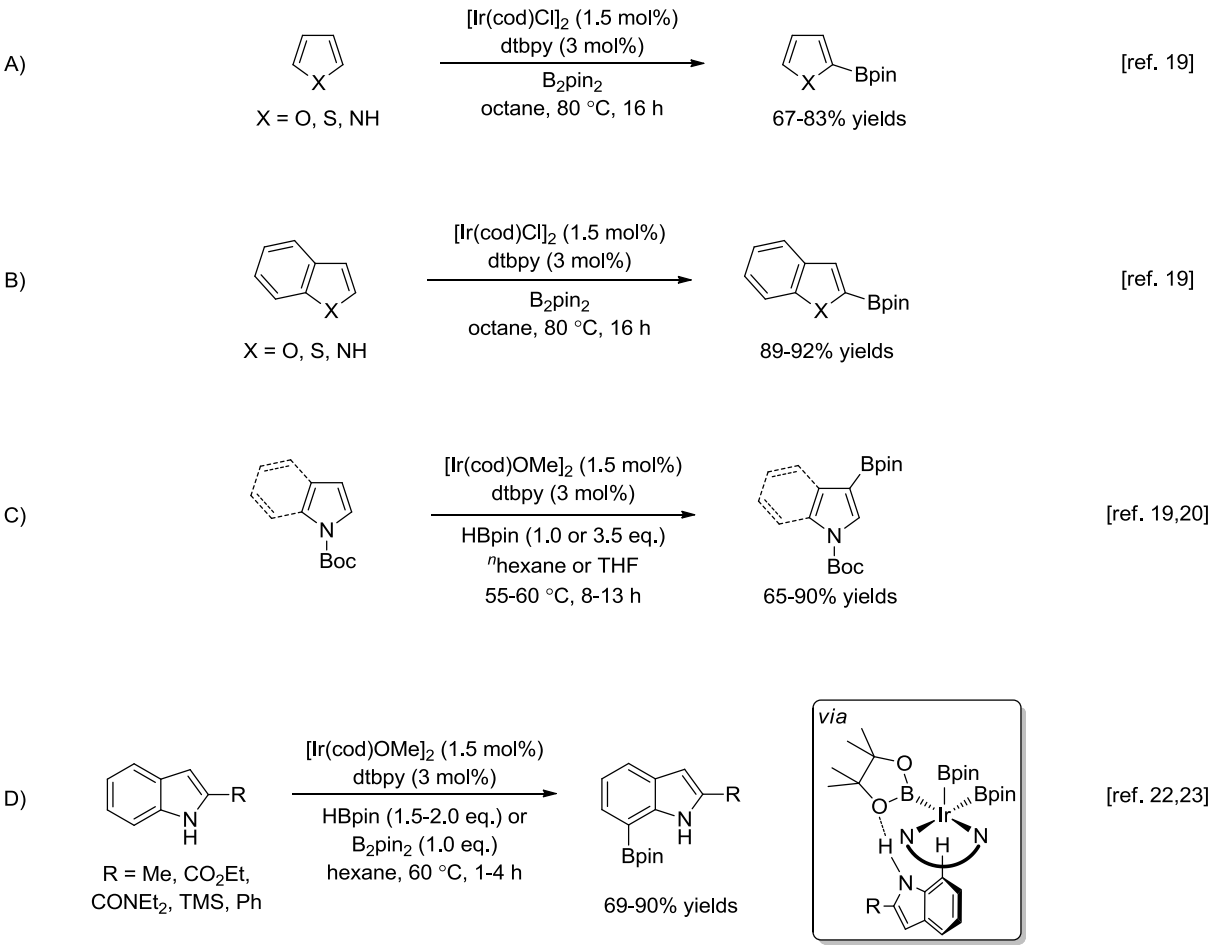
The regioselectivity of the iridium-catalysed aromatic C-H borylation employing bipyridyl ligands is predominantly controlled by steric effects. As a general rule, borylation *ortho* to a substituent or ring junction is usually avoided. When multiple unhindered C-H bonds are present, the borylation reaction occurs with equal probability at each of these positions. The borylation of monosubstituted benzenes, for example, typically gives *meta* and *para* products in an approximately 2:1 ratio (***Scheme 31A***).[10] Symmetrical 1,2-disubstituted and 1,3-disubstituted benzenes lead to a single product (***Schemes 7B-C***).[11] In the absence of unhindered C-H bonds, for example 1,4-disubstituted benzenes, borylation occurs preferentially *ortho* to the smaller substituent (***Scheme 31D***).[18]



Scheme 31. Regioselectivity in the borylation of disubstituted benzenes.

In the absence of steric effects, electronic effects are observed, particularly in heteroaromatic systems. Unsubstituted five-membered ring heteroaromatics for example, react much faster than benzene and borylate alpha to the heteroatom (***Scheme 32A***).[19] The higher reactivity of electron-rich heteroaromatics contradicts Smith's observation that electron-poor carbocyclic arenes react faster than electron-rich carbocylic arenes.[10] Benzofused derivatives also show a similar selectivity with preferential borylation occurring at the 2-position of the heterocyclic ring (***Scheme 32B***).[19] If the 2-position is sterically hindered by a bulky N-protecting group then borylation occurs in the heterocyclic ring at the 3-position (***Scheme 32C***).[19,20] Interestingly, a 2-substituted indole undergoes borylation in

the carbocyclic ring at C-7, presumably *via* N-H coordination to a boryl group on the iridium catalyst (***Scheme 32D***).[21-23]

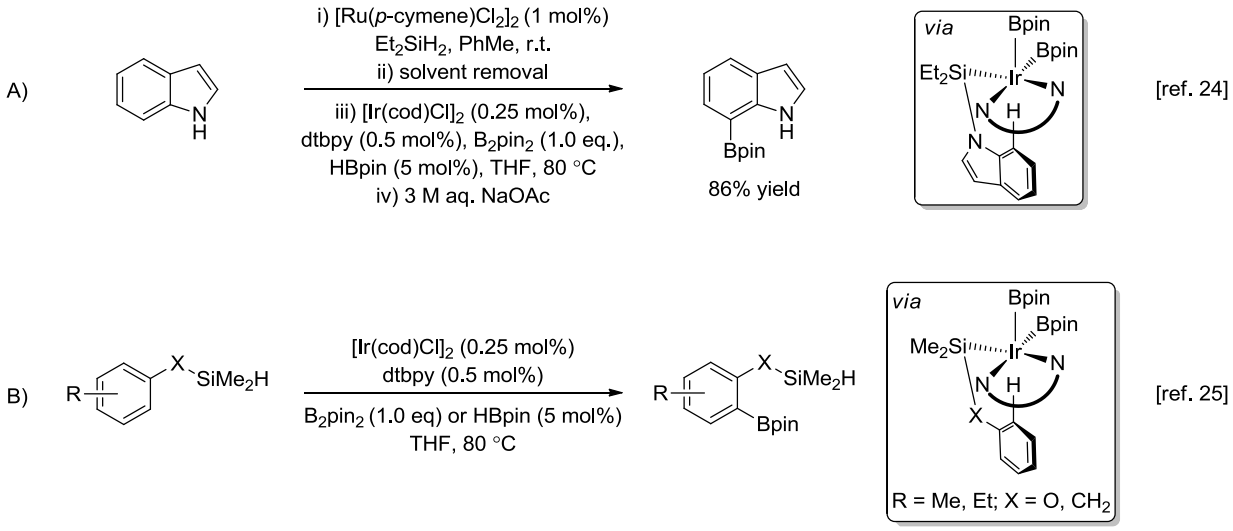


Scheme 32. Borylation of 5-membered ring heteroaromatics.

The regioselectivity of pyridine borylation is distinctly different to pyrrole, wherein borylation alpha to the nitrogen is generally avoided. For a more detailed discussion on this, see Chapter 3.

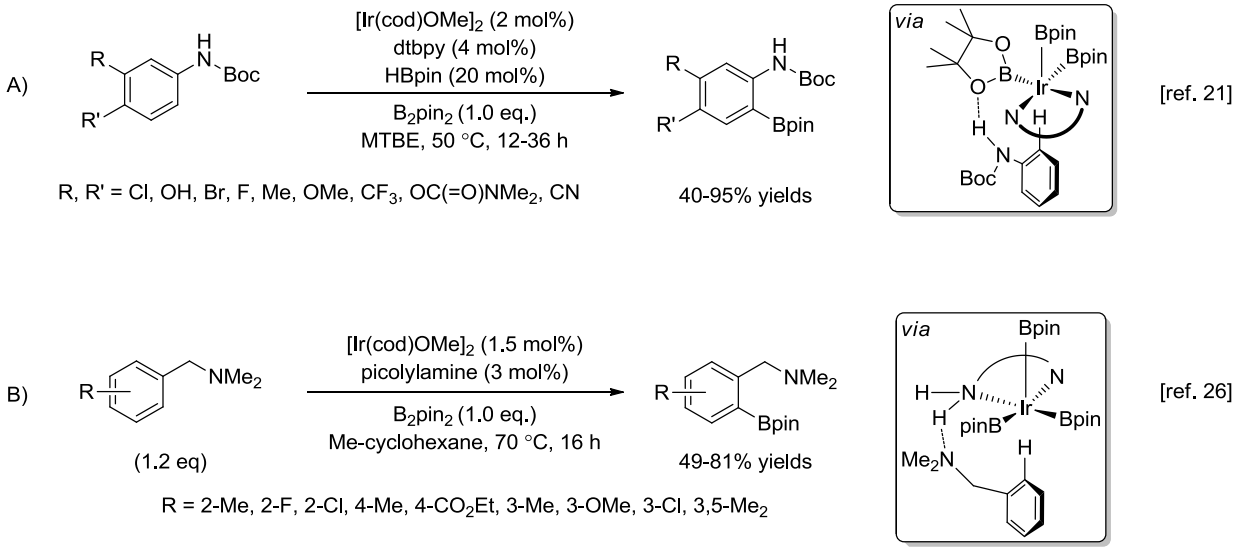
2.1.4 Directing Effects

In an analogous fashion to 2-substituted pyrrole, *N*-dialkylsilyl indoles undergo borylation at C-7, this time *via* a silyl-iridium coordination (***Scheme 33A***).[24] Similar directing effects have also been achieved in carbocyclic arenes using benzylic and phenolic dialkylhydrosilanes (***Scheme 33B***).[25]



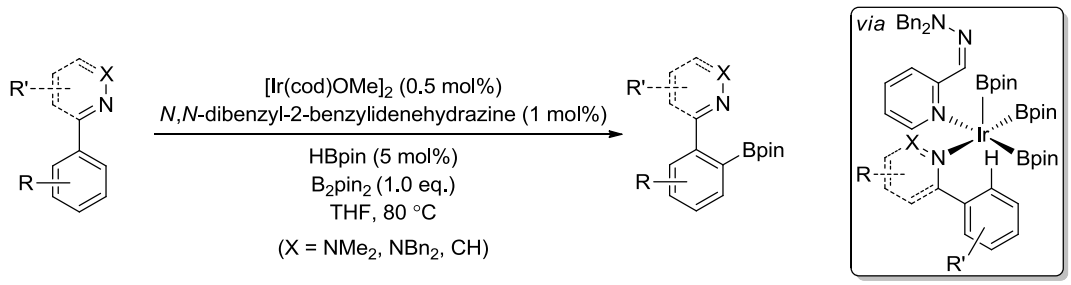
Scheme 33. *Ortho* -directed borylation of benzyl and phenolic dialkoxysilanes.

Recently, substrate-ligand interactions have been exploited to direct borylation *ortho* to *N*-Boc and benzylic amine groups (***Scheme 34***).[21,26]



Scheme 34. *Ortho*-borylation of *N*-Boc-anilines and benzylic amines.

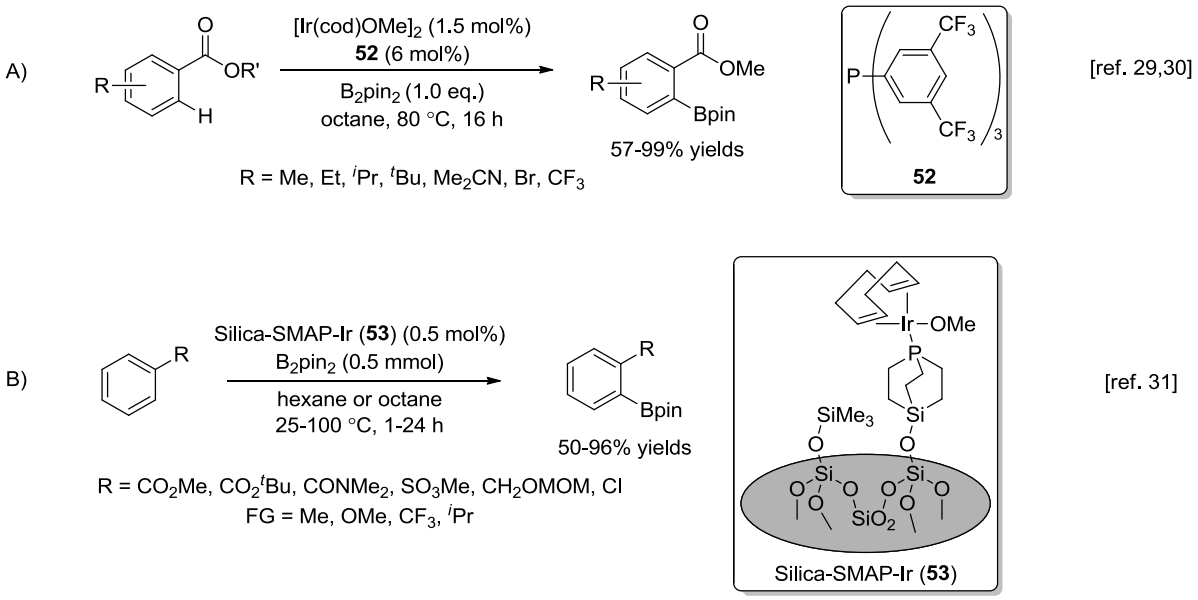
Pyridine-hydrazone *N*,*N*-ligands can also be used to direct borylation *ortho* to hydrazones (***Scheme 35***).[27,28] In these reactions, reversible coordination between the labile hydrazone to the ligand and the iridium catalyst leads to intermittent coordination of the hydrazone of the borylation substrate resulting in activation of an adjacent C-H bond on the neighbouring ring.



Scheme 35. *Ortho*-borylation of phenyl hydrazones.

Ishiyama, Miyaura and co-workers showed that monodentate phosphine ligands such as tris(3,5-bis(trifluoromethyl)phenyl)phosphine (**52**) can also be used with similar effects,

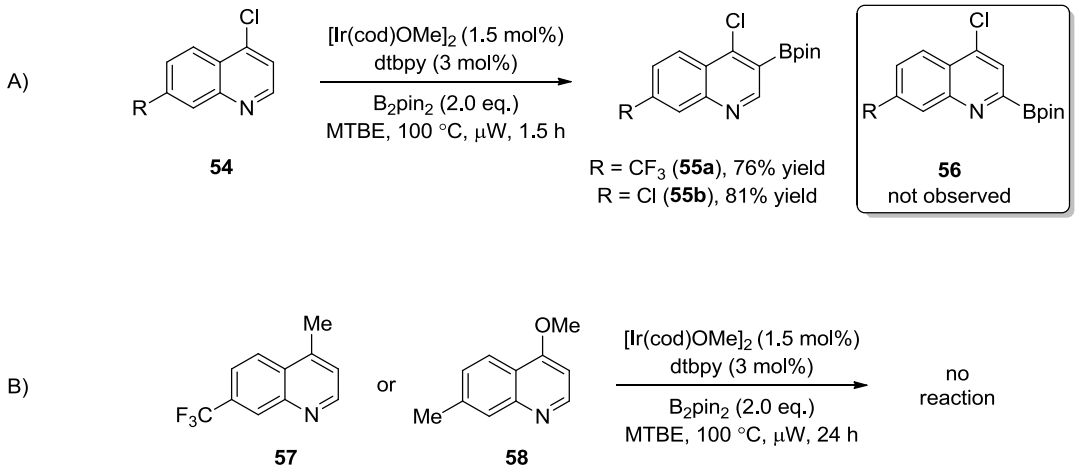
leading to *ortho*-borylation of alkyl benzoates (***Scheme 36A***).[29,30] A similar directing effect for a wide range of other *ortho*-directing groups have been reported using polymer supported Silica-SMAP-Ir (**53**) (***Scheme 36B***).[31] This has since been successfully applied to 5-membered ring heteroaromatics[32] and phenyl carbamates.[33]



Scheme 36. *Ortho*-borylation of alkyl benzoates using a monodentate phosphine ligand.

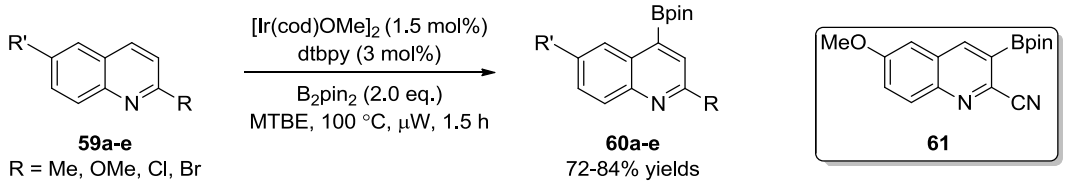
2.2 Previous Work and Project Goals

Previously in the group, P. Harrisson explored the iridium-catalysed aromatic C-H borylation as a method for selective functionalisation of important quinoline motifs.[34] From these studies, interesting electronic effects were observed in the borylation of a range of disubstituted quinolines. The reactions of sterically encumbered 4,7-disubstituted quinolines, for example, afforded the 3-borylated product when the 4-position is occupied by a chlorine atom (***Scheme 37A***) but no reaction was observed with the more sterically demanding methoxy and methyl groups (***Scheme 37B***). The reason for the lack of borylation at the 2-position in these reactions is not clear, especially as the reported borylation of analogous 4,4'-di-*tert*-butyl-2,2'-bipyridine proceed smoothly alpha to the pyridyl nitrogen.[35]



Scheme 37. Borylation of 4,7-disubstituted quinolines.

Borylation of 2,6-disubstituted quinolines is favoured on the heterocyclic over the carbocyclic ring and with a preference for C-H bonds adjacent to ring junctions over positions adjacent to substituents (***Table 2***).



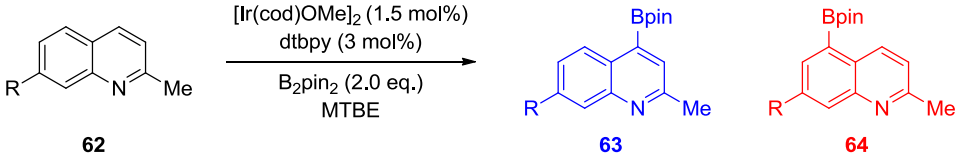
entry	**59**	R	R'	yield **60** (%)
1	**a**	Me	Me	72
2	**b**	Me	OMe	76
3	**c**	Me	Cl	79
4	**d**	Me	Br	84
5	**e**	CN	OMe	98[a]
6	**e**	CN	OMe	83[b]

[a]A mixture of **60e** and **61** (85:15) was observed; [b]reaction run at r.t. for 48 h.

Table 2. Borylation of 2,6-disubstituted quinolines.

Continuing with this trend, 7-substituted quinaldines typically give 4- and 5-borylated products in favour of the former (***Table 3***). Enhanced regioselectivity is observed at room temperature. However, the reaction does not function below 0 ˚C. Interestingly, 7-chloroquinaldine (**62f**) borylates exclusively at the 5-position in the carbocyclic ring to give **64f** in 81% isolated yield (***Table 3***, entry 11). This unusual regiochemistry was confirmed by obtaining a crystal structure of the 5-borylated product. Such an observation was particularly difficult to rationalise when compared with the results for the bromo and trifluoromethyl analogues (***Table 3***, entries 9, 10, 12 and 13). If, however, this could be understood through electronic effects, it could potentially be exploited to enable further control of regioselectivity beyond the use of steric effects alone. Importantly, the ability to use both steric and electronic effects to define and control regioselectivity would increase the versatility of iridium-catalysed aromatic C-H borylation for selective functionalisation of arenes. In order to achieve this, the subsequent section describes initial efforts to obtain

further insights regarding the electronic parameters that govern the borylation regioselectivity in the absence of steric effects.



62 63 64

entry	62	R	temp.[a] (˚C)	time (h)	conv. (%)[b]	ratio[c] **63** : **64** : other	yield (%)[d]
1	**a**	Me	100	1	88	82 : 12 : 6	nd
2	**a**	Me	r.t.	72	93	> 95 : < 5	80
3	**b**	OMe	100	1.5	>95	90 : 10 : 0	nd
4	**b**	OMe	r.t.	48	89	> 95 : < 5	73
5	**c**	CN	100	0.25	>95	82 : 9 : 9	nd
6	**c**	CN	r.t.	48	92	> 95 : < 5	86
7	**d**	TMS	100	1.5	85	70 : 20 : 10	nd
8	**d**	TMS	r.t.	72	91	85 : 10 : 5	68
9	**e**	Br	100	1.5	80	65 : 35	nd
10	**e**	Br	r.t.	48	90	80 : 20	65[e]
11	**f**	Cl	100	1.5	>95	> 5 : < 95	81
12	**g**	CF_3	100	1.5	>95	60 : 40	nd
13	**g**	CF_3	r.t.	20	94	70 : 30	65[f]

[a]Reactions were either run at room temperature or at 100 °C under microwave heating; [b]conversion determined by GC-MS; [c]product ratios determined by GC-MS; [d]isolated yield of major isomer, unless otherwise stated, nd = not determined; [e]minor isomer isolated in 15% yield; [f]minor isomer isolated in 27% yield.

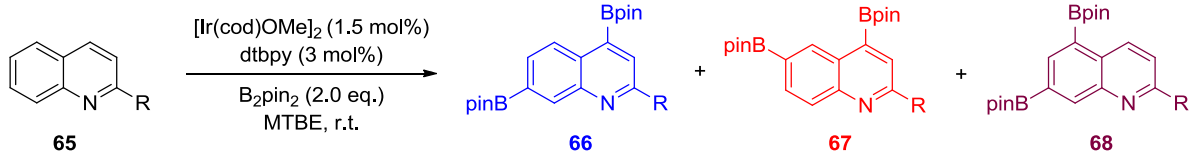
Table 3. Borylation of 2,7-disubstituted quinolines.

2.3 Results and Discussion

Given the preference for borylation of the heterocyclic over carbocyclic ring in the quinoline derivatives above, it was of interest to examine if similarly high electronically-guided regioselectivity exists on the less sterically encumbered 2-substituted quinolines.

2.3.1 Borylation of 2-Substituted Quinolines

The borylation of 2-substituted quinolines was initially conducted using the same conditions as reported by Harrisson.[36] This involved charging a crimp top microwave vial with the substrate followed by purging with argon and the addition of an aliquot of preformed stock solution of the catalyst containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%), MTBE (2.4 mL) and B_2pin_2 (1.0 eq.). The tubes were then heated in a focused microwave reactor at 80 ˚C for 1.5 hours before they were quenched with dichloromethane and concentrated under reduced pressure to give a complex and intractable mixture containing multiple mono- and bisborylated products (GC-MS and TLC). The quenching mode of action of dichloromethane is not well understood; however, this effect has been previously observed on numerous occasions within the group. In order to simplify the analysis, reactions were run at room temperature with an excess of B_2pin_2 leading to the formation of a mixture of three major bisborylated products (GC-MS). Careful analysis of the crude mixtures using COSY, HSQC and HMBC NMR spectroscopic techniques revealed that the mixture contained 4,6- and 4,7-bisborylated isomers **66** and **67**, accompanied by a small amount of the 5,7-isomer **68** (***Table 4***).



			GC-MS	^{1}H NMR ratio
65	R	time (h)	conv. (%)	**66** : **67** : **68**
a	Me	24	>95	68 : 32 : 0
b	CF_3	5	90	51 : 42 : 7

Table 4. Borylation of 2-substituted quinolines with excess B_2pin_2.

Identification of these products was primarily based on a combination of HMBC correlation of a distinctive $^{13}\underline{C}F_3$ or $^{13}\underline{C}H_3$ signal to 3-H and the upfield shift of protons adjacent to newly formed C-B bonds (***Figure 1***). The lack of a boryl group in the heterocyclic ring of product **68b** for example, was determined on the basis that a distinctive $^{13}CF_3$ quintet showed an HMBC correlation to a 3-H <u>doublet</u> rather than a singlet at δ 7.76 ppm. In addition, there is a correlation in the COSY between this doublet and another highly deshielded doublet at δ 9.34 ppm consistent with an upfield shift of 4-H by approximately 1.0 ppm, arising from the introduction of a boronate at a *peri* 5-position. The protons at δ 8.58 ppm and δ 8.83 ppm have similar integral values and showed a weak complementary w-coupling, suggesting that the remaining boryl group must be at the 7-position. This assignment was consistent with upfield shift of 6-H and 8-H by approximately 0.5 and 1.0 ppm respectively. In an analogous fashion to **68b**, HMBC correlation of each of the two remaining $^{13}CF_3$ groups to two different <u>singlet</u> 3-H suggests the presence of a boronate in the heterocyclic ring for both of the remaining isomers. Careful analysis of the proton chemical shifts in these products led to putative structures consistent with **66b** and **67b**.

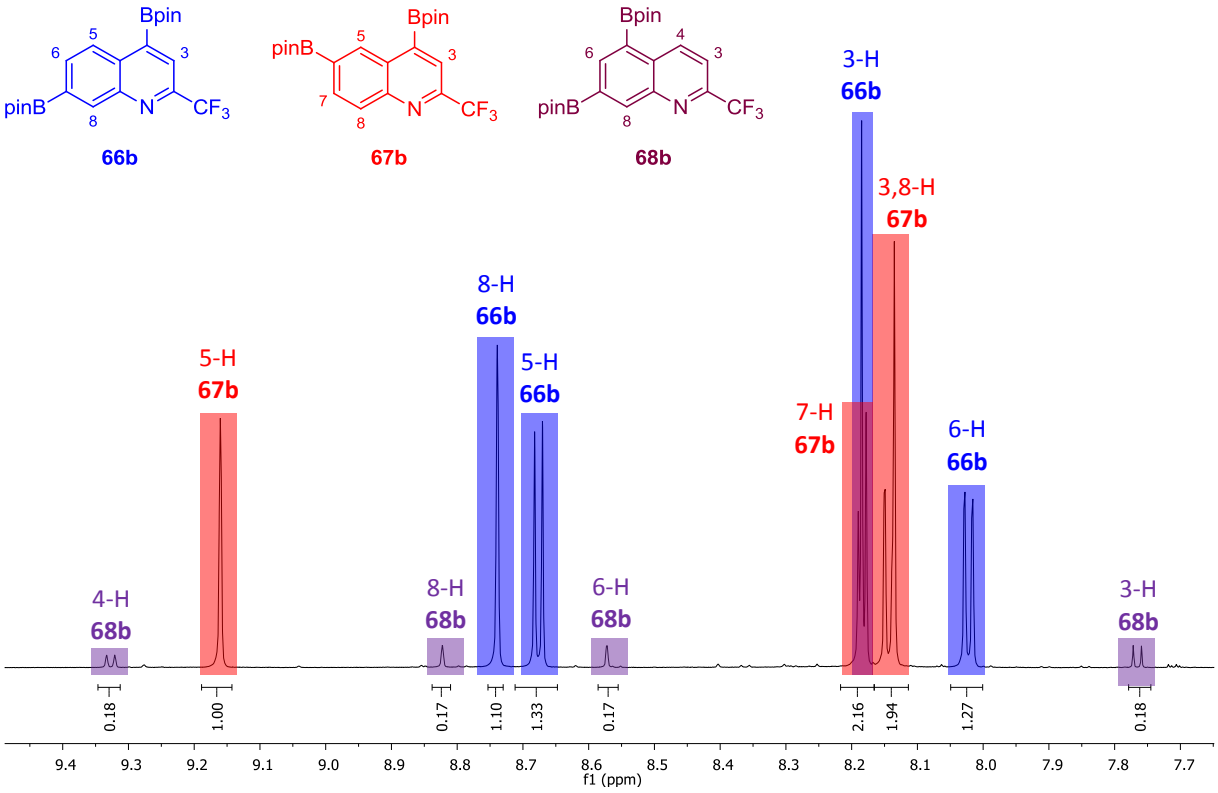
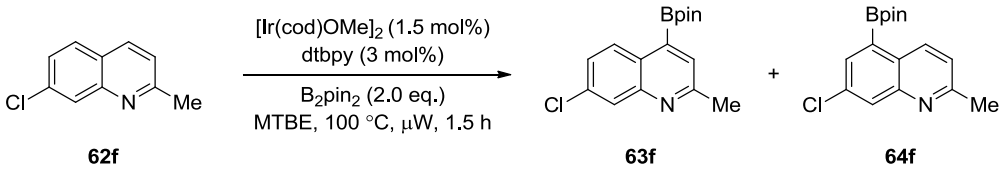


Figure 1. ^{1}H NMR spectrum of the 2-(trifluoromethyl)quinoline crude borylationmixture.

The absence of product **68a** from the borylation of quinaldine (**65a**) and its trace formation from the borylation of 2-(trifluoromethyl)quinoline (**65b**) suggests that the initial borylation occurs preferentially at the 4-position in the heterocycle. Interestingly, there is also a preference for the subsequent borylation of the 7-position over the sterically equivalent 6-position, an effect that was diminished in the presence of an electron-withdrawing group at the 2-position. These results suggest that the high selectivity between sterically equivalent C-H bonds in either heterocyclic/carbocyclic or carbocyclic/carbocyclic systems could be intrinsically linked to the same underlying electronic effects.

2.3.2 Borylation of 7-Chloroquinaldine

Given the general preference for 2-substituted quinolines and 2,7-disubstituted quinolines to borylate at the heterocylic over carbocyclic ring, the unusual regioselectivity in the borylation of 7-chloroquinaldine (**62f**) reported by Harrisson[34] was investigated. Initial work involved repeating the borylation experiment using identical conditions (***Scheme 38***).



Scheme 38. Borylation of 7-chloroquinaldine under microwave heating.

Analysis of the crude mixture by GC-MS showed a single product peak on the TIC trace exhibiting a single chlorine isotope pattern with peaks at *m*/*z* = 303.1 and 305.1, consistent with a monoborylated product (***Figure 2***).

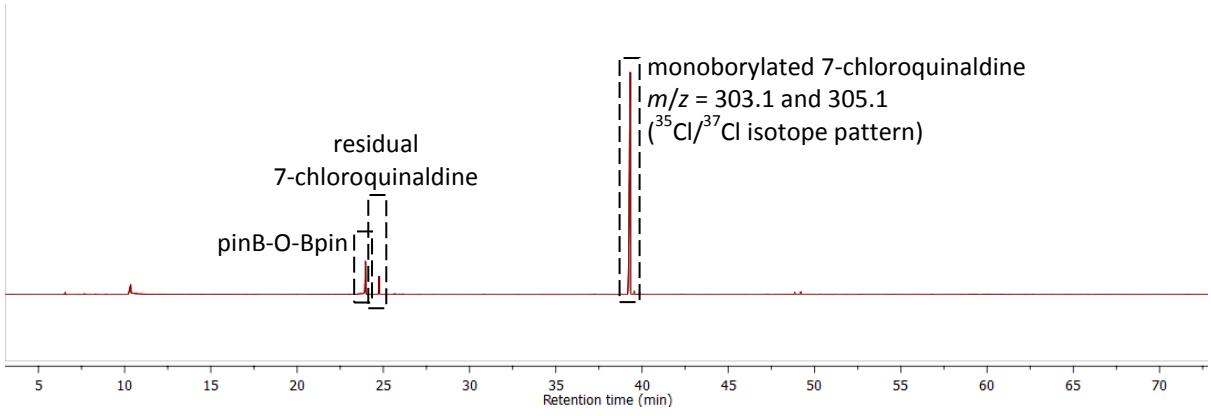


Figure 2. GC-MS TIC trace of 7-chloroquinaldine crude borylation mixture.

Analysis of the same mixture by ^{1}H NMR spectroscopy, however, showed two possible monoborylated products in approximately 2:1 ratio with the minor isomer consistent with Harrisson's reported 5-borylated product **64f**. Subsequent flash column chromatography using a Teledyne Isco Combiflash®Rf following Harrisson's purification protocol showed a large sharp absorption followed by a weaker and much broader absorption peak in the UV-trace under short (254 nm), long (280 nm) and broad (200-360nm) UV-detection mode (***Figure 3***).

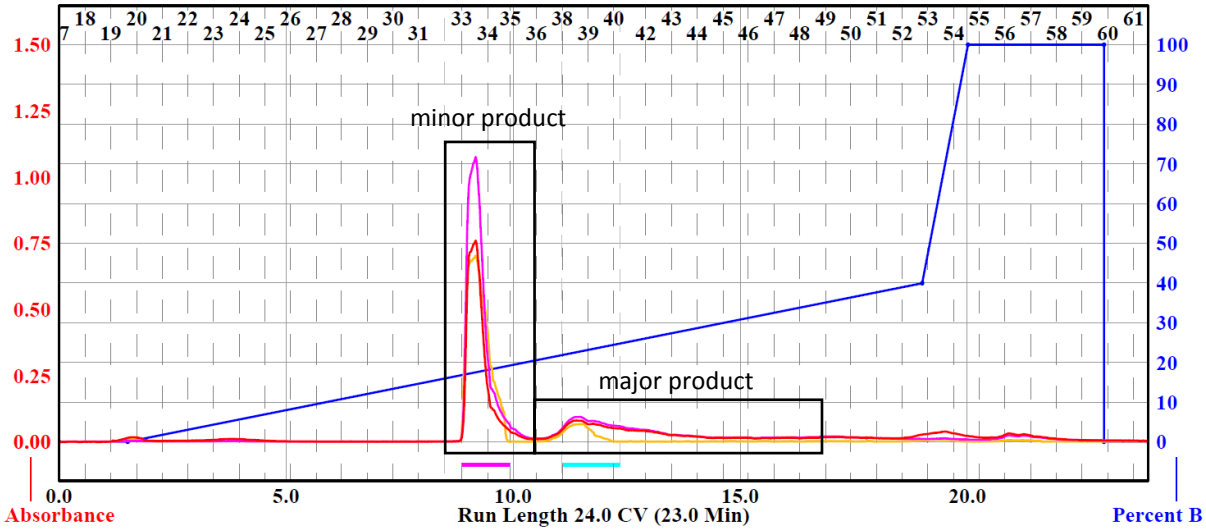


Figure 3. UV-absorption on flash column chromatography of 7-chloroquinaldine crude borylation mixture.

The fractions (32-35) containing strongly absorbing material were concentrated and following recrystallisation from acetonitrile, gave **64f** in 11% yield. The loss of 5-H signal and the highly shifted signals for 4-H (δ 8.93 ppm) and H-6 (δ 8.09 ppm) in the ^{1}H NMR spectrum were consistent with the introduction of an adjacent (*ortho*) boronate group and the data reported by Harrisson (***Figure 4***). Concentration of fractions 36-48, however, afforded **63f** in

61% yield. Formation of the 4-borylated product could be clearly ascertained from the ^{1}H NMR spectrum, by the loss of the 4-H signal and a distinctive shift to higher frequency of the signals for 3-H (δ 7.74 ppm) and 5-H (δ 8.53 ppm) (***Figure 4***). These assignments were confirmed through COSY, HSQC and HMBC experiments with the HMBC correlation between a distinctive CH_3 carbon signal and either a singlet 3-H in **63f** or a doublet 3-H in **64f** being particularly diagnostic.

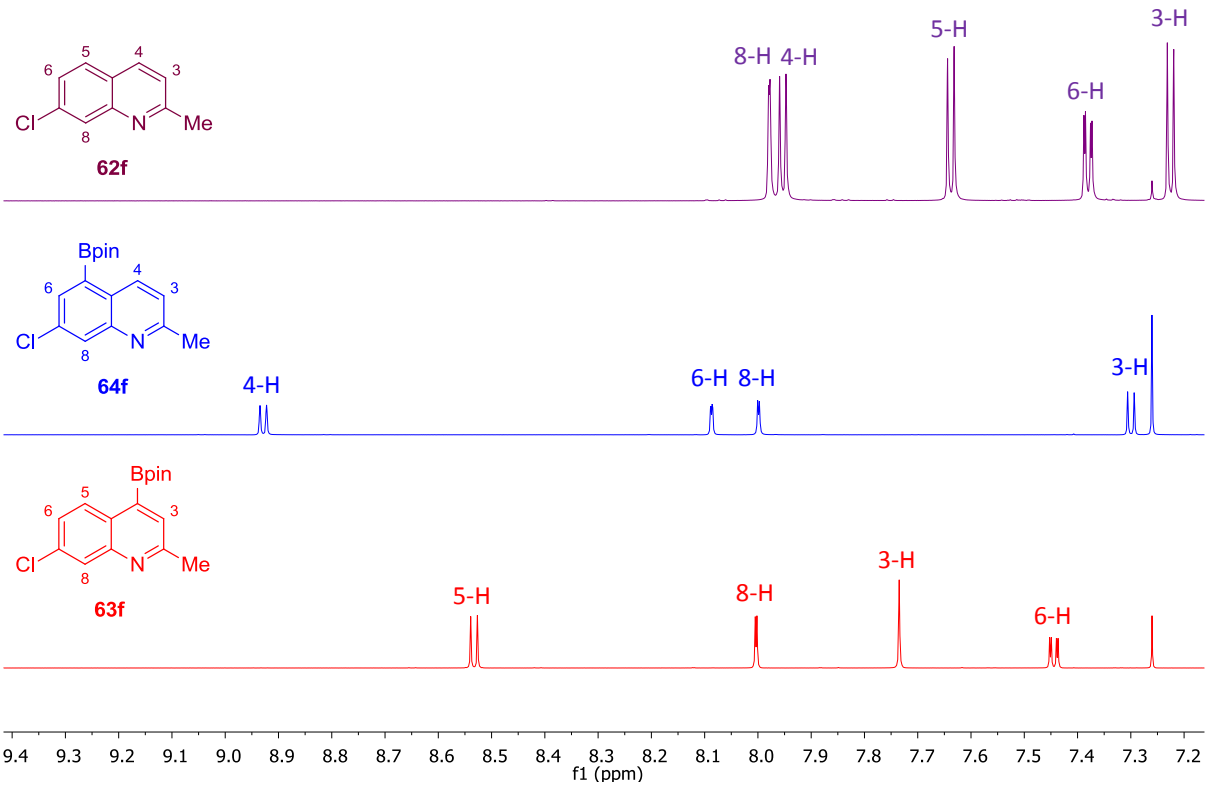
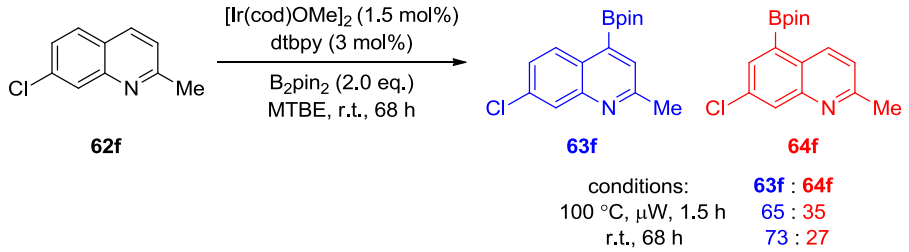


Figure 4. ^{1}H NMR spectra of 7-chloroquinaldine and its borylated products.

This observation of a 65:35 mixture of 4-:5- borylated products was in stark contrast to the 5:95 ratio reported by Harrisson. An improved regioselectivity of 73:27 was obtained when

the reaction was repeated at room temperature, consistent with the temperature-regioselectivity effects observed with other 7-substituted quinaldines (***Scheme 39***).

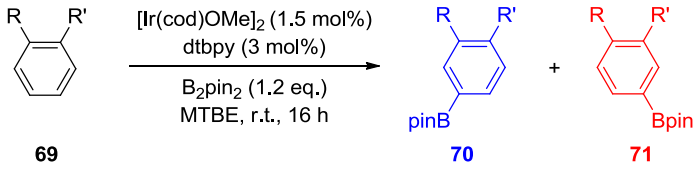


Scheme 39. Borylation of 7-chloroquinaldine.

These new results were subsequently confirmed by an independent collaborator, S. Kawamorita, in Germany. The difference between the regioselectivity observed here and that reported in Harrisson's thesis is not understood. One reason could be a misinterpretation of the TIC trace of the GC-MS of the crude mixture, which appeared to indicate a single product. The UV-trace of the flash column chromatography also appeared to suggest, and led to, the isolation of the minor isomer, **64f**, as a single product. This, however, could not account for the high reported yield of 81% in Harrisson's thesis. Nonetheless, the corrected regioselectivity reported herein provides a more consistent trend in the borylation of 7-substituted quinaldines. This trend is better observed at room temperature and revealed a range of directing effects. In the absence of steric factors, borylation preferentially occurs on the heteroaromatic ring rather than the carbocyclic ring. However, the presence of a strongly inductive electron-withdrawing group at C-7 resulted in significant levels of borylation at the sterically equivalent C-5 position.

2.3.3 Borylation of 1,2-Disubstituted Benzenes

Having confirmed that electronic parameters could have a distinctive effect on the regiochemical outcome of borylation reactions when conducted at room temperature, it was speculated that similar electronically-guided regioselectivity could be observed in unsymmetrical 1,2-disubstituted benzene derivatives. Consequently a series of substrates was examined for selectivity at both elevated temperature and at room temperature. While at elevated temperatures these substrates give a near 1:1 mixture of products, reactions at room temperature led to mixtures of the two isomers in unequal amounts (***Table 5***).



69 **70** **71**

					^{1}H NMR ratio
entry	**69**	R	R'	conv. (%)	**70** : **71**
1	**a**	OMe	Cl	94	60 : 40
2	**b**	OMe	Me	75	75 : 25
3	**c**	OMe	CO_2Me	>99	85 : 15
4	**d**	OMe	COMe	>99	89 : 11
5	**e**	Me	Cl	>99	34 : 66
6	**f**	Me	COMe	87	56 : 44
7	**g**	Me	CN	>99	60 : 40
8	**h**	Me	CO_2Me	>99	73 : 27
9	**i**	-$CH_2CH_2CH_2CO$-		>99	80 : 20
10	**j**	Cl	COMe	>99	62 : 38
11	**k**	Cl	Bpin	>99	84 : 16
12	**l**	CO_2Me	Bpin	35	53 : 47

Table 5. Borylation of 1,2-disubstituted benzenes.

Due to the high volatility of the substrates, reaction conversions were calculated by GC-MS analysis of the quenched reaction mixtures prior to concentration. Separation of the regioisomers proved to be difficult and so the isomeric ratios were calculated by NMR analysis of either the crude reaction mixture or the reaction mixture *in-situ*. One exception to this is the borylation of **69l**, which gave convoluted ^{1}H NMR spectrum both *in-situ* and as a crude mixture. The isomeric ratios were consequently calculated based on GC-MS analysis of the crude mixture, which was tentatively assigned based on the selectivity trend observed with other 1,2-disubstituted benzenes. The calculation of isomeric ratio *in-situ* for some of the other reactions exploits the homogeneity of the borylation reaction mixtures. This involves conducting the reaction in an NMR tube containing a coaxial acetone-d_6 solvent stick. Acetone-d_6 was chosen for its high deuterium loading, which helps with locking the deuterium signal in the presence of a substantial amount of protiated MTBE solvent. This method is particularly useful for substrates that give a convoluted crude ^{1}H NMR spectrum in $CDCl_3$, as well as ketone-containing substrates such as **69f** and **69j**, which can undergo reduction to the corresponding alcohol when the reaction mixture is subjected to work-up. The mechanism for such reduction is not well understood; however, an iridium(I) trisboryl complex has been previously shown to facilitate transfer hydrogenation of carbonyls in the presence of H_2 donors such as methanol or isopropanol (see Chapter 4.3.5).[37] A combination of 1D and 2D NMR spectroscopic experiments (COSY, HSQC, HMBC and NOESY) enabled resonances to be assigned unambiguously to individual isomers. For example, the reaction of 2-methylbenzonitrile (**69g**) produced a 52:40 mixture of two monoborylated isomers accompanied by a small amount (8%) of the 3,5-bisborylated product **72** (***Figure 5***).

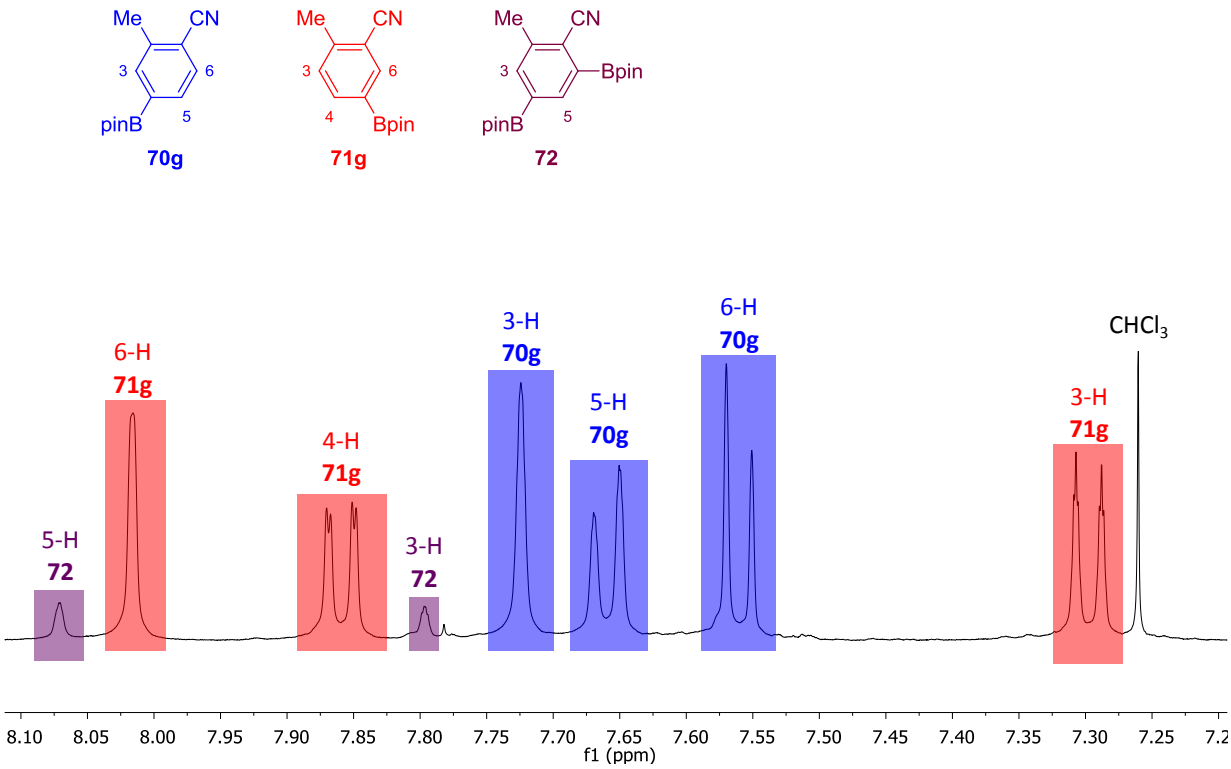


Figure 5. ^{1}H NMR spectrum of 2-methyl benzonitrile crude borylation mixture.

The formation of this last product reflects the relatively low steric requirements of the cyano group. The minor monoborylated isomer **71g** was deduced to be the 5-borylated product by virtue of the appearance of a highly de-shielded peak at δ 8.02 ppm, corresponding to the hydrogen mutually *ortho* to both the nitrile and boronate ester, showing a weak three-bond coupling to a doublet of doublets for the hydrogen at C-4 at δ 7.86 ppm. In contrast, the major C-4-borylated isomer **70g** showed a similar shift to the higher frequency of the hydrogens adjacent to the boronate ester, but in this case corresponding to H-3 (δ 7.72 ppm) and H-5 (δ 7.66 ppm), the latter showing coupling to the hydrogen *ortho* to the nitrile at δ 7.56 ppm. This assignment was confirmed by a NOESY correlation between the singlet at δ 7.72 ppm and the Ar-CH_3 group at δ 2.53 ppm, while a similar link could be made between

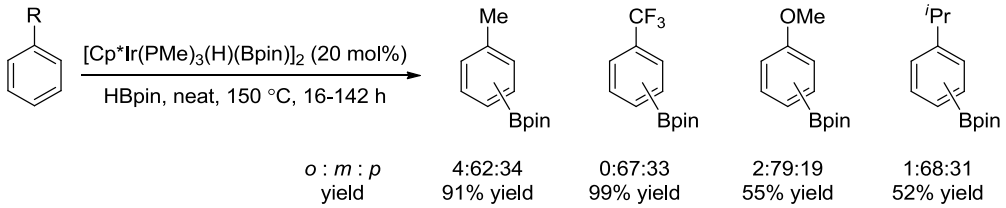
the alternative methyl singlet at δ 2.54 ppm and the H-3 doublet of the minor isomer at δ 7.30 ppm.

These experiments lead to a general observation that while π-electron acceptors (-M) such as CO_2Me, and strong σ-donors (+I) such as Bpin, favour borylation at the *para* position, π-donors (+M) such as Cl, and σ-electron withdrawing groups (-I) direct borylation towards the *meta* position. These directing effects are in direct contrast to electrophilic aromatic substitution whereby groups that donate electron density to the ring act as *ortho*/*para* directors whilst groups that withdraw electron density from the ring act as *meta* directors. If this electronically-guided selectivity could be further improved, then the borylation of arenes could serve to complement electrophilic aromatic substitution for the selective functionalisation of a wide range of aryl C-H bonds.

2.3.4 Borylation of Monosubstituted Benzenes

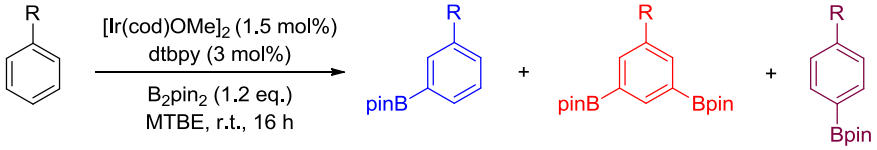
In order to further investigate and thus establish an empirical hierarchy of these electronic directing effects, the product ratios obtained from the borylation of a series of monosubsituted benzenes were re-examined in the hope that by undertaking these experiments at room temperature, similar electronically guided selectivities could be observed. Literature reports on the relative selectivities of iridium-catalysed borylation of monsubstituted arenes have been limited to reactions at high temperatures with, in most

cases, regiochemistry not substantially different from the commonly reported 2:1 statistical ratio of *meta:para* products (***Scheme 40***).[10,38-40]



Scheme 40. Borylation of monosubstituted benzenes.

One noticeable exception to this is the preference for the *meta*-borylation of anisole, which is commonly attributed to the coordination of the methoxy group to the iridium catalyst leading to the activation of C-3.[40] In this study, the borylation of monosubstituted benzenes at room temperature was carried out in a similar fashion to the borylation of 1,2-disubstituted benzenes (***Table 6***).



73 **74** **75** **76**

			^{1}H NMR δ (ppm)			conv.	^{1}H NMR ratio	m:p ratio
entry	**73**	R	o	m	p	(%)	**74** : **75** : **76**	(**74**+**75**) : **76**
1	**a**	$Bmes_2$	7.51	7.34	**7.47**	69	26 : 6 : 68	32 : 68
2	**b**	Bneop	7.81	7.36	**7.44**	45	33 : 0 : 67	33 : 67
3	**c**	Bpin	7.82	7.38	**7.48**	71	32 : 4 : 64	36 : 64
4	**d**	CO_2Me	7.97	7.37	**7.47**	>99	22 : 22 : 56	44 : 56
5	**e**	CN	7.65	7.46	**7.60**	>99	30 : 36 : 34	59 : 41
6	**f**	$Si(TMS)_3$	7.44	7.24	**7.24**	72	48 : 15 : 37	63 : 37
7	**g**	Cl	7.29	7.24	7.17	98	32 : 33 : 35	65 : 35
8	**h**	Me	7.06	**7.14**	7.04	30	63 : 6 : 31	69 : 31
9	**i**	CF_3	7.64	7.49	7.56	>99	29 : 40 : 31	69 : 31
10	**j**	TMS	7.68	**7.44**	7.44	93	56 : 16 : 28	72 : 28
11	**k**	^{t}Bu	7.28	**7.18**	7.05	82	68 : 8 : 24	76 : 24
12	**l**	NMe_2	6.60	**7.08**	6.59	69	75 : 4 : 21	79 : 21
13	**m**	OMe	6.78	**7.17**	6.82	93	68 : 16 : 6	84 : 16

Table 6. Borylation of monosubstituted benzenes.

As such, the conversions of these reactions were also calculated based on GC-MS analysis of the quenched reaction mixture, prior to concentration. The conversions with respect to non-volatile $PhBmes_2$ (**73a**), PhBneop (**73b**), and PhBpin (**73c**), however, were more conveniently calculated alongside analysis of the products isomer distribution from the ^{1}H NMR spectrum of the crude mixture. Product structural assignments using a combination of ^{1}H NMR, ^{13}C NMR, COSY, HSQC and HMBC experiments revealed that these reactions proceed to give a 3,5-bisborylated product **75a-m** in addition to the expected *meta* and *para* products (**74a-m** and **76a-m** respectively). The formation of *para* product **76i**, for example, was initially

identified on the basis that two doublets with similar integral values at δ 7.60 ppm and δ 7.91 ppm show COSY to each other but not to signals in other regions of the ^{1}H NMR spectrum (***Figure 6***). This assignment was confirmed by an HMBC correlation between a distinctive $^{13}CF_3$ signal and the less deshielded of the two sets of doublets. In addition, the upfield shift of the more deshielded protons is consistent with an introduction of a boronate on the adjacent C-4. Similar rationale follows the identification of **74i** and **75i** with coupling patterns key to their initial assignment.

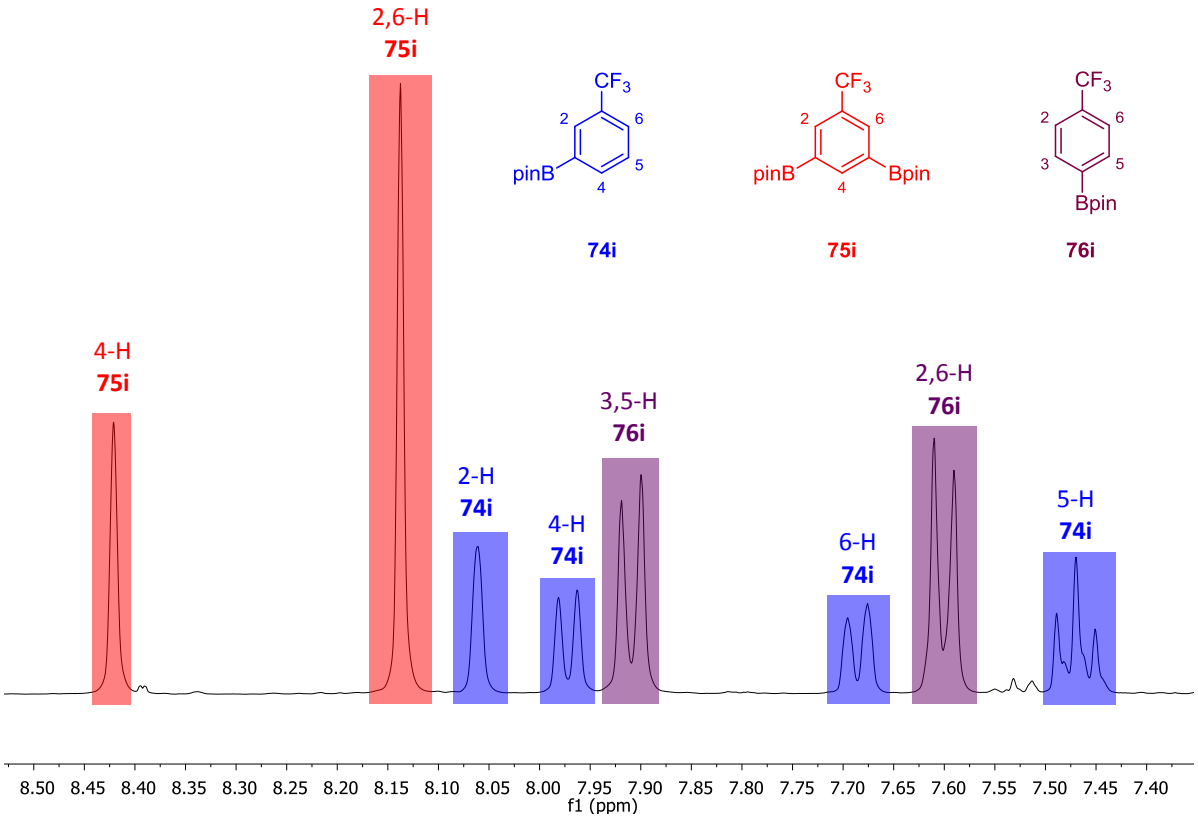


Figure 6. ^{1}H NMR spectrum of (trifluoromethyl)benzene crude borylation mixture.

By assuming that the bisborylated products **75a-m** arise from initial borylation at the *meta* position, the underlying *m:p* selectivity ratios can then be determined. Satisfyingly,

significant deviations from the 2:1 statistical ratio typically observed at elevated temperatures were found for all substrates (***Table 6***). These deviations matched the findings from the 1,2 series, with π-accepting groups (-M) such as CO_2Me, and strong σ-donors (+I) such as $Bmes_2$, Bneop and Bpin, leading to enhanced *para* selectivity (***Table 6***, entries 1-4), while chlorobenzene, N,N-dimethylaniline and anisole (+M, -I) all underwent increased *meta* borylation (***Table 6***, entries 7, 12 and 13). Further analysis of these results showed a good correlation between ^{1}H and ^{13}C NMR shift patterns of the starting arene (determined experimentally) and the preferred site of borylation. With the exception of the benzonitrile (**73e**), for which a significant amount of *ortho* borylation is observed,[18] and trifluoromethylbenzene (**73i**), the electronically preferred site for borylation appears to correspond to the most deshielded of the *meta* and *para* hydrogen atoms. A similar situation exists for all the quinoline analogues and 1,2-disubstituted benzenes studied (***Figure 9***). This simple predictive test is also valid for all of the other substrates explored, for example the ratio of isomers arising from the bisborylation of 2-(trifluoromethyl)quinoline (**65b**) (***Figure 1***) correlating with the chemical shifts in the starting material (***Figure 7***). Thus, the most deshielded protons are the most likely to be substituted on electronic grounds once simple steric effects and statistical factors are taken into account.

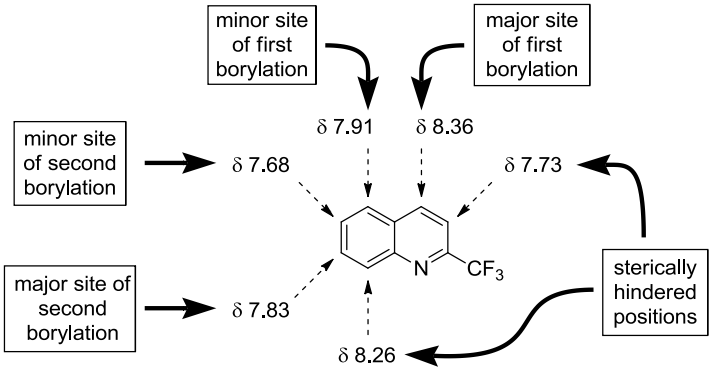


Figure 7. Correlation of borylation regiochemistry with ^{1}H NMR chemical shift as typified for 2-(trifluoromethyl)quinoline.

2.3.5 C-H Acidity

Although valuable as a predictive tool, the NMR-regiochemistry correlation is only qualitative as the difference in chemical shifts (Δδ) and the observed quantitative selectivity do not appear to be related (***Figure 8***).

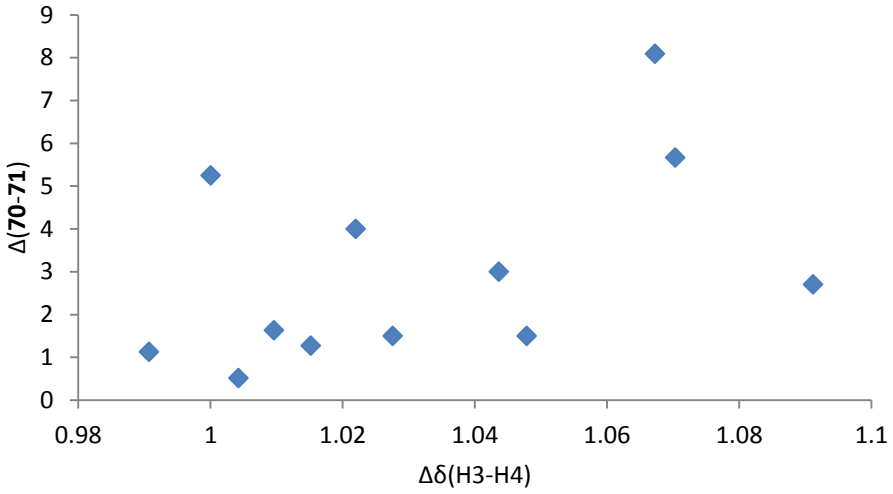
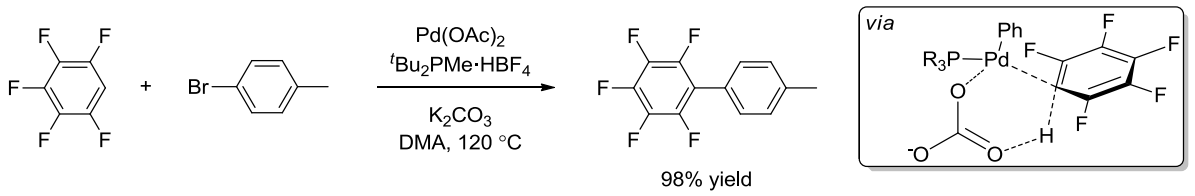


Figure 8. Difference in ^{1}H NMR chemical shifts vs. borylation regioselectivity.

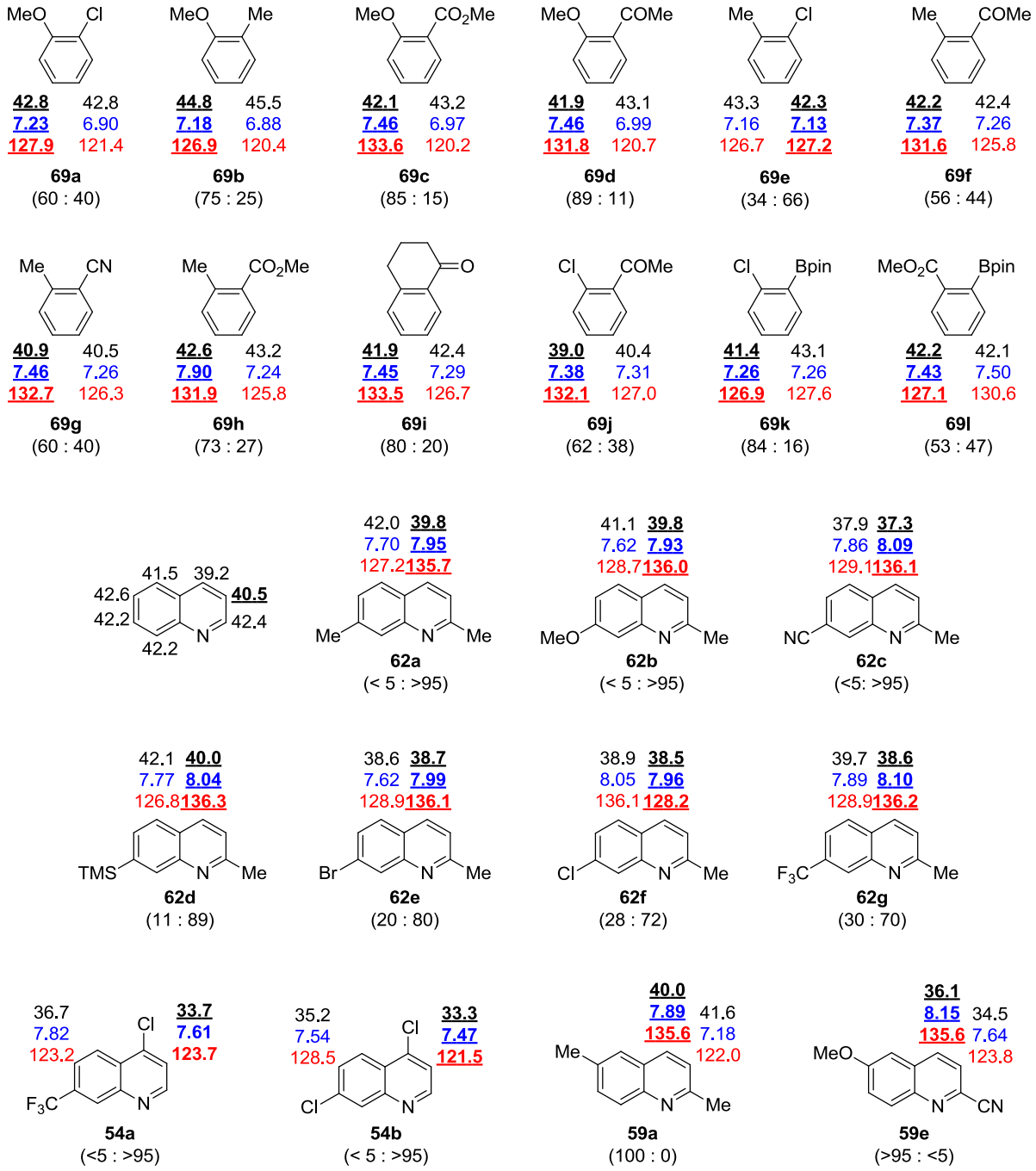
Consequently, C-H acidity was considered as a related physicochemical parameter in an effort to provide a better prediction of selectivity. Such involvement of C-H acidity would be consistent with Smith and Hartwig's suggestions that the activation of C-H bonds proceed through σ-bond metathesis rather[41,42] than oxidative addition.[17] This pathway, in which an IrHBpin adduct is formed, suggests that a basal boryl ligand might effectively 'deprotonate' a C-H bond of an Ir-H bound arene.[41] This is related to the ligand-assisted depotonation mechanism frequently invoked in other transition metal-catalysed C-H activation processes, in which C-H acidity has also been suggested to be a selectivity driving force. For example, in palladium-catalyzed C-H arylation of fluorine-containing arenes, C-H acidities provided good correlations with site selectivities.[43-46] In many of these palladium examples, a ligand can function as a base in the key C-H activation step (***Scheme 41***).



Scheme 41. Ligand-assisted C-H activation as described by Fagnou *et. al.*

In contrast, in C-H borylation reactions, the electrons in the M-B σ-bond could formally deprotonate an Ir-complexed arene. Moreover, recent studies on Ir-catalyzed C-H borylation, particularly those relating to heteroarene substrates, have also suggested that C-H acidity may contribute to regiochemical selectivity.[18,41] Such an observation would also fit with the observed higher reactivity of heteroarenes in the Ir-catalyzed aromatic C-H borylation reaction when compared with their carbocyclic counterparts, as the former have

uniformly lower pK_a values. On this basis, and as NMR chemical shifts can be related to C-H acidities, collaborative work was initiated with Professor Lin at Hong Kong University of Science and Technology. Using Guo's p*K*a prediction model, Professor Lin obtained pK_a values for compounds in solution (***Figure 9***).[49] Reflecting the NMR shift values, there is very close correlation between the site of highest C-H acidity and the position of preferred borylation of 1,2-disubstituted benzenes. Although a similar link can also be seen in the quinoline series, the model does not fully account for the increasing amounts of borylation at C-5 as the 7-substituent has an increasingly larger inductive electronic effect (CF_3 > Cl > Br).

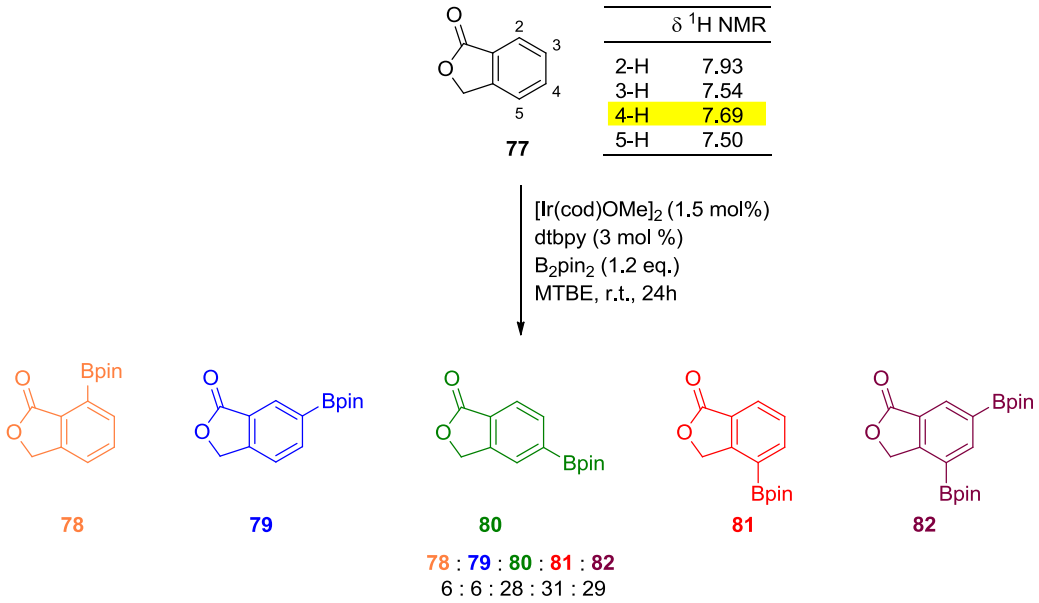


pK_a (black); ^{1}H NMR (blue); ^{13}C NMR (red); **predominant position of borylation is indicated as bold and underlined numbers**

Figure 9. Calculated pK_a values, ^{1}H NMR and ^{13}C NMR chemical shifts and regioselectivity in the room temperature Ir-catalyzed borylation of 1,2-disubstituted arenes and quinolines.

2.3.6 Testing the C-H Acidity Hypothesis: Borylation of Phthalide

To test the hypothesis that the borylation of arenes is contingent on C-H acidity in the absence of steric effects, and that the regiochemistry can simply be predicted from the ^{1}H NMR spectrum of the starting material, the borylation of phthalide at room temperature was undertaken. The reaction was conducted in an NMR tube containing a co-axial acetone-d_6 solvent stick and monitored *in-situ* by ^{1}H NMR spectroscopy. Analysis of ^{1}H and ^{13}C NMR spectra of the phthalide starting material indicates that borylation between the only two unhindered sites would be favoured at the more deshielded proton at the 4-position over the 3-position (***Scheme 42***).



Scheme 42. Borylation of phthalide.

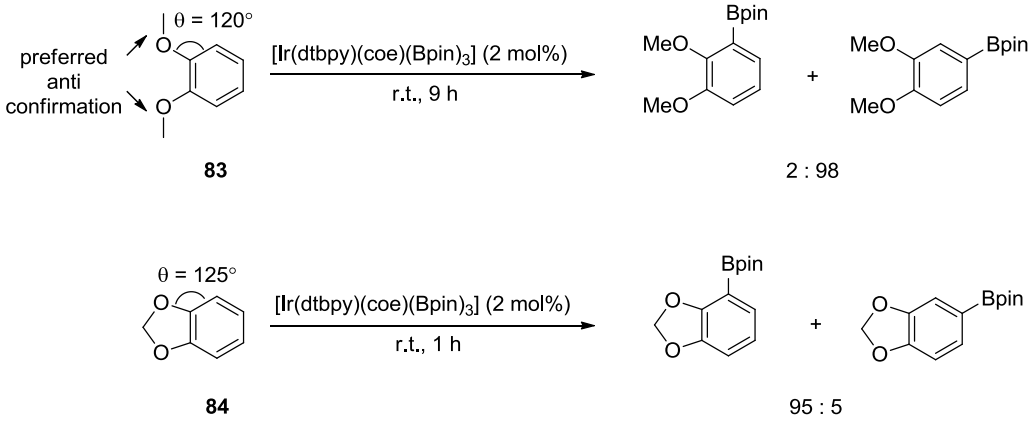
Experimentally however, significant borylation of the 2- and 5-positions (**78** and **81**, respectively) was also observed along with some 3,5-bisborylated product **82** (***Scheme 42***).

The structural assignments were confirmed by COSY, HSQC and HMBC experiments in a similar fashion to the products obtained from the borylation of 1,2-disubstituted benzenes in Section 2.3.3. In order to simplify analysis, the relative ratio of **79**, **81** and **82** were monitored over time (***Table 7***). The similar rate in the formation of the bisborylated product (**82**) and the fall in the amount of **81** suggests that **82** was likely to form as a result of the second borylation of **81**. The rise in the formation of **79** on the other hand, is more sluggish and is unlikely to contribute significantly to the formation of **82**.

		product ratio		
entry	time (h)	**79**	**81**	**82**
1	1	6	87	6
2	17	13	53	34
3	24	17	39	45

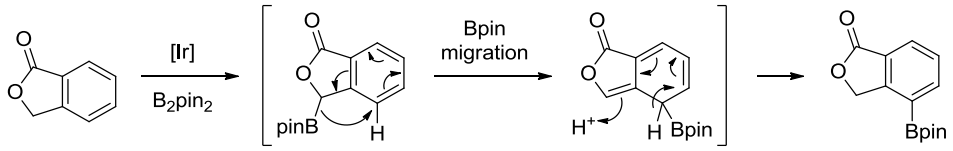
Table 7. Relative ratios of products in the borylation of phthalide as a function of time.

Following these assumptions, the underlying selectivity for the borylation of 2-, 3-, 4, and 5-positions becomes 6:6:28:60. The significant borylation of 2-H and 5-H may be attributed to the less sterically demanding *ortho* substituents as they are tied back in a 5-ring system. This effect has been previously observed between the borylation of veratrole (**83**) and the related benzodioxole (**84**) (***Scheme 43***).[41]



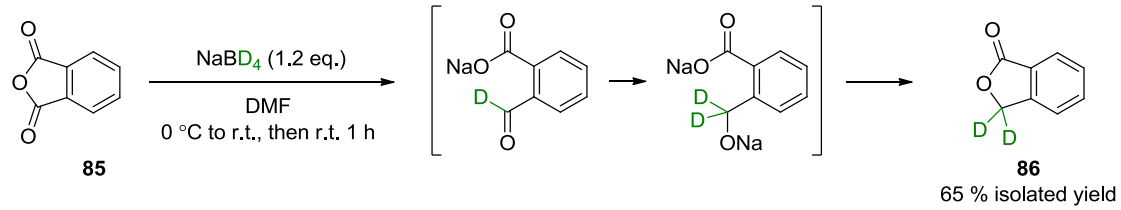
Scheme 43. Borylation of veratrole and benzodioxole.

This however, cannot account for the preferential borylation of 5-H, which is less deshielded than the protons at the 2- and 3-positions. One possible explanation could be an initial borylation of a benzylic CH_2 followed by Bpin migration (***Scheme 44***).



Scheme 44. Proposed mechanism for theunprecedented borylation of phthalide at the 5-position.

In order to investigate this, phthalide-d_2 (**86**) was synthesised in good yield from the reduction of phthalic anhydride (**85**) with $NaBD_4$ (***Scheme 45***).[50,51] The mechanism for this reduction proceed *via* double reduction of one of the carbonyls to give a primary alcohol, which then attacks the carbocylic acid to give the desired lactone.



Scheme 45. Reduction of phthalic anhydride with $NaBD_4$.

The signal for benzylic CD_2 could be seen in the ^2D NMR spectrum of the product at δ 5.35 ppm (***Figure 10***). By comparing the integral of the residual benzylic CH_2 with the aromatic region of the ^1H NMR spectrum an excellent deuterium level of 99.6% was found.

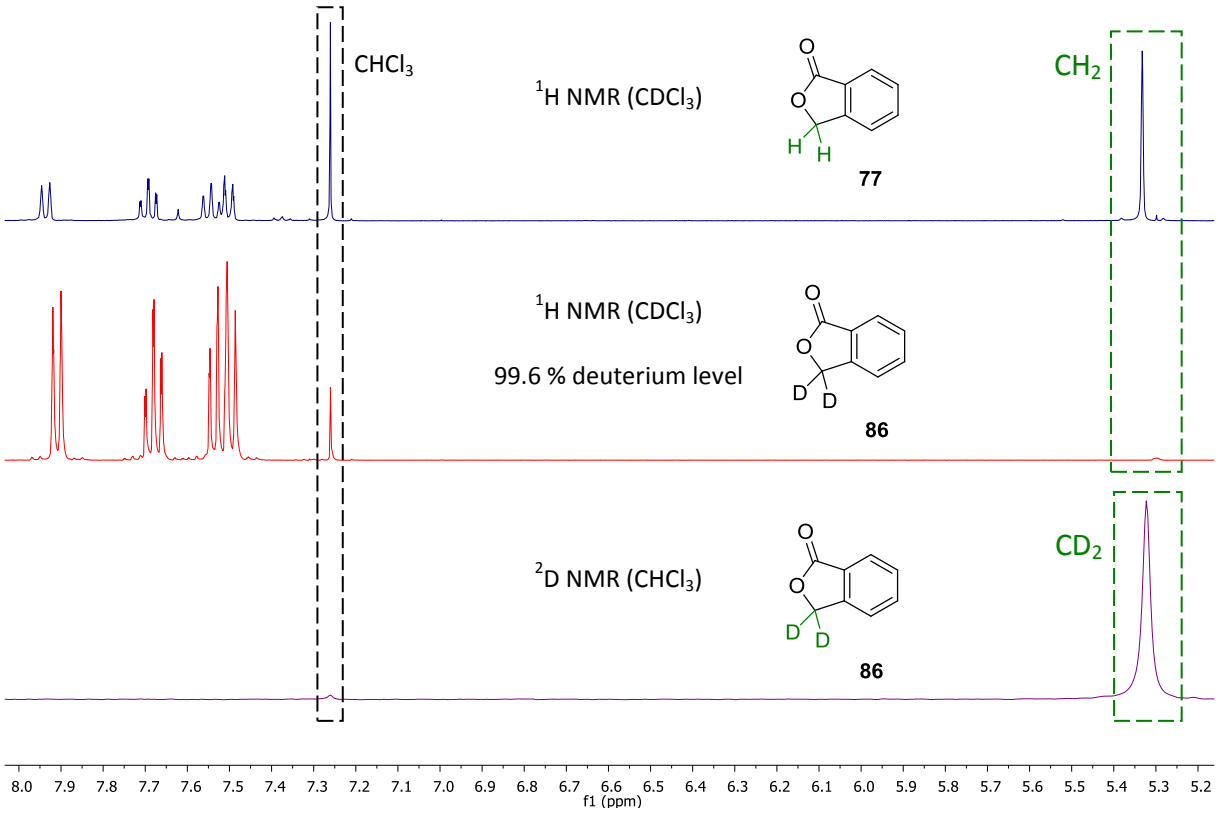


Figure 10. Evidence for benzylic CD_2 in phthalide-d_2.

Subsequent borylation of phthalic anhydride at room temperature however, did not lead to an increase in benzylic C-H signal in the ^{1}H NMR spectrum of the reaction mixture *in-situ*. This suggests that the migration mechanism proposed in ***Scheme 44*** could not have occurred and that other electronic factors such as coordination of the carbonyl to the iridium complex or to a boryl ligand must be involved. The borylation of the related open-chain methyl 2-(acetoxymethyl)benzoate (**87**) could offer further insight. The larger steric bulk of these groups, however, would most likely hinder borylation at the 5-position altogether.

2.4 Conclusions

Once steric factors have been taken into account, NMR chemical shift analysis of substrates can be used to predict the preferred site of iridium-catalyzed borylation from a range of unhindered C-H bonds in both arene and heteroarenes. Although the reaction is often carried out at elevated temperatures, enhanced regioselectivity can be achieved at lower temperatures, allowing the underlying electronic effects to become more evident. This electronic selectivity appears to be diametrically opposed to that observed in electrophilic aromatic substitution reactions with π-electron withdrawing group favoring *para* substitution and inductive electron-withdrawing groups and π-electron donating groups leading to enhanced *meta* substitution. Consistent with this, transfer of negative charge from Ir to arene has been suggested to be a key factor in these C-H borylations.[41] While C-H acidity appears to provide a qualitative measure of this selectivity, the correlation is not perfect and alternative factors may be more important, for example in the borylation of phthalide. Further experimental and theoretical studies of regioselectivities, as well as the development of more-active catalysts is required to exploit this effect in unencumbered substrates.

2.5 References

[1] Nguyen, P.; Blom, H. P.; Westcott, S. A.; Taylor, N. J.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 9329.

[2] Waltz, K. M.; He, X. M.; Muhoro, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11357.

[3] Waltz, K. M.; Muhoro, C. N.; Hartwig, J. F. *Organometallics* **1999**, *18*, 3383.

[4] Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2009**, *110*, 890.

[5] Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 7696.

[6] Chen, H. Y.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391.

[7] Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.

[8] Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168.

[9] Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305.

[10] Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.

[11] Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056.

[12] Yinghuai, Z.; Yan, K. C.; Jizhong, L.; Hwei, C. S.; Hon, Y. C.; Emi, A.; Zhenshun, S.; Winata, M.; Hosmane, N. S.; Maguire, J. A. *J. Organomet. Chem.* **2007**, *692*, 4244.

[13] Frey, G. D.; Rentzsch, C. F.; von Preysing, D.; Scherg, T.; Muhlhofer, M.; Herdtweck, E.; Herrmann, W. A. *J. Organomet. Chem.* **2006**, *691*, 5725.

[14] Tagata, T.; Nishida, M. *Adv. Synth. Catal.* **2004**, *346*, 1655.

[15] Murata, M.; Odajima, H.; Watanabe, S.; Masuda, Y. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1980.

[16] Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.

[17] Tamura, H.; Yamazaki, H.; Sato, H.; Sakaki, S. *J. Am. Chem. Soc.* **2003**, *125*, 16114.

[18] Chotana, G. A.; Rak, M. A.; Smith, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 10539.

[19] Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.

[20] Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199.

[21] Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2012**, *134*, 11350.

[22] Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552.

[23] Lo, W. F.; Kaiser, H. M.; Spannenberg, A.; Beller, M.; Tse, M. K. *Tetrahedron Lett.* **2007**, *48*, 371.

[24] Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068.

[25] Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534.

[26] Roering, A. J.; Hale, L. V. A.; Squier, P. A.; Ringgold, M. A.; Wiederspan, E. R.; Clark, T. B. *Org. Lett.* **2012**, *14*, 3558.

[27] Ros, A.; Estepa, B.; Lopez-Rodriguez, R.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11724.

[28] Ros, A.; López-Rodríguez, R.; Estepa, B.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 4573.

[29] Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535.

[30] Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159.

[31] Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058.

[32] Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855.

[33] Yamazaki, K.; Kawamorita, S.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3978.

[34] Harrisson, P. PhD, Durham University, 2011.

[35] Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489.

[36] Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586.

[37] Tajuddin, H.; Shukla, L.; Maxwell, A. C.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2010**, *12*, 5700.

[38] Zhu, Y. H.; Chenyan, K.; Peng, A. T.; Emi, A.; Monalisa, W.; Louis, L. K. J.; Hosmane, N. S.; Maguire, J. A. *Inorg. Chem.* **2008**, *47*, 5756.

[39] Rentzsch, C. F.; Tosh, E.; Herrmann, W. A.; Kuhn, F. E. *Green Chemistry* **2009**, *11*, 1610.

[40] Cho, J. Y.; Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 12868.

[41] Vanchura, I. I. B. A.; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, J. R. E.; Singleton, D. A.; Smith, I. I. I. M. R. *J. Chem. Soc., Chem. Commun.* **2010**, *46*, 7724.

[42] Webster, C. E.; Fan, Y. B.; Hall, M. B.; Kunz, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 858.

[43] Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Transactions* **2009**, 5820.

[44] Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

[45] Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

[46] Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

[47] Dang, L.; Lin, Z. Y.; Marder, T. B. *J. Chem. Soc., Chem. Commun.* **2009**, 3987.

[48] Zhu, J.; Lin, Z. Y.; Marder, T. B. *Inorg. Chem.* **2005**, *44*, 9384.

[49] Shen, K.; Fu, Y.; Li, J. N.; Liu, L.; Guo, Q. X. *Tetrahedron* **2007**, *63*, 1568.

[50] Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574.

[51] Vitullo, V. P.; Sridharan, S.; Johnson, L. P. *J. Am. Chem. Soc.* **1979**, *101*, 2320.

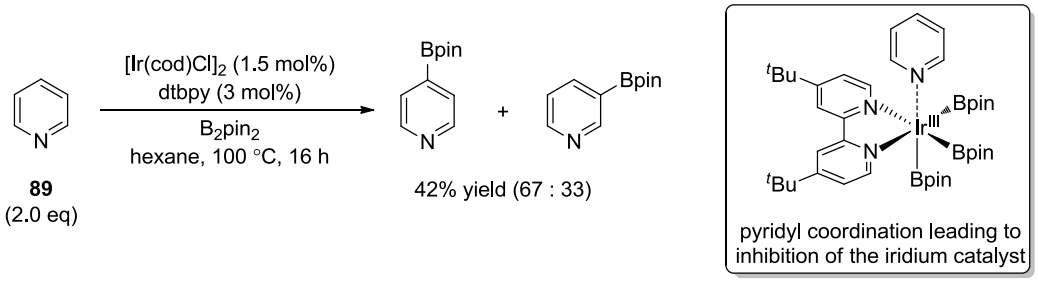
Chapter 3 - Borylation of Pyridine Derivatives

3.1 Introduction

It was shown in the previous chapter that the regioselectivity of the iridium-catalysed aromatic C-H borylation is contingent on C-H acidity in the absence of steric effects. Following on from this, work in this chapter is directed towards the exploration of these electronic effects for the synthesis of α-pyridyl boronate esters.

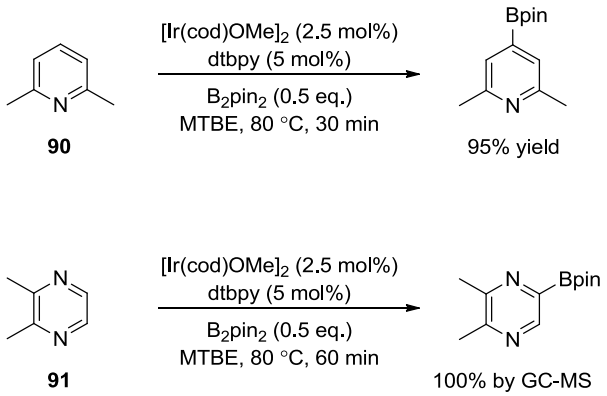
3.2 Literature Background

Five-membered ring heteroaromatics such as pyrrole, borylate rapidly and exclusively at the 2-position, alpha to the heteroatom. The borylation of analogous unsubstituted pyridine (**89**) however, is much slower and gives 4- and 3-borylated products in a statistical 2:1 ratio, akin to the borylation of monosubstituted benzenes (***Scheme 46***).[1,2] This lower reactivity and yield can be attributed to coordination of the pyridyl nitrogen to, and hence inhibition of, the iridium catalyst by blocking access to the required site for C-H activation.[2,3]



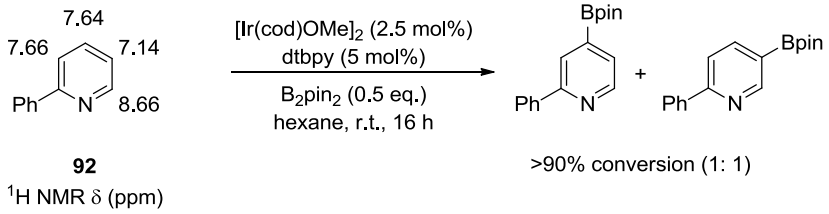
Scheme 46. Borylation of unsubstituted pyridine.

Consistent with this, disruption of the pyridyl coordination by one or two *ortho* substituents allows the borylation reaction to proceed very readily, for example in the borylation of 2,6-dimethylpyridine (**90**) and 2,3-dimethylpyrazine (**91**) (***Scheme 47***).[4]



Scheme 47. Borylation of 2,6-dimethylpyridine and 2,3-dimethylpyrazine.

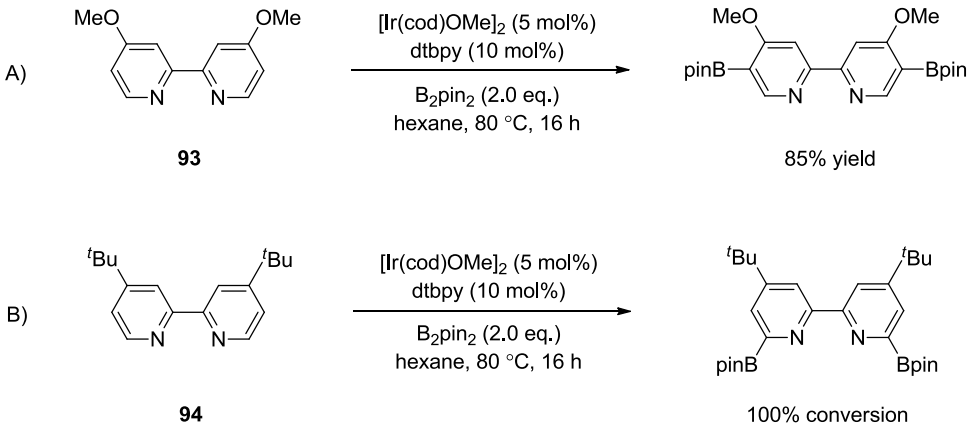
Interestingly, the analogous 2-phenylpyridine (**92**) borylates at the 4- and 5-positions whilst the sterically equivalent 6-position remained unaffected (***Scheme 48***).[5] The complete lack of borylation at this most deshielded proton, alpha to the pyridyl nitrogen, cannot be explained by simple steric effects arising from the proposed pyridyl coordination.



Scheme 48. Borylation of 2-phenylpyridine.

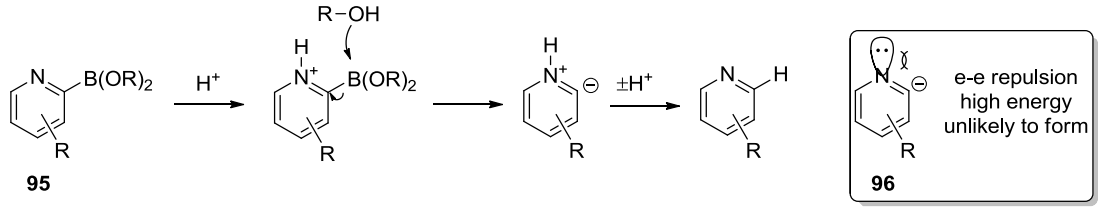
Hartwig initially proposed that coordination of the pyridyl nitrogen to a boron atom of B_2pin_2 could account for this observation. However, Santos and Marder have independently

demonstrated that a solution of 4-picoline and B_2pin_2 does not lead to the formation of a tetravalent boron adduct.[6,7] A more likely scenario could involve the formation of a partial negative charge on the aryl carbon during the deprotonation step of C-H activation. This is consistent with computational studies, which demonstrates that the oxidative addition of aryl C-H bonds proceed with significant proton transfer character.[3] The formation of such a transition state is therefore unfavourable in the presence of a neighbouring pyridyl lone pair due to coulombic repulsion. To overcome this electronic effect, extremely large steric groups are required to block the 4- and 5-positions. For example, whereas 4,4'-dimethoxy-2,2'-bipyridyl (**93**) leads to the borylation at 3- and 3'-positions (***Scheme 49A***), borylation proceeds at C-6, alpha to the nitrogen when the methoxy groups are replaced with significantly larger *tert*-butyl groups (***Scheme 49B***).[5] Disruption of the pyridyl coordination by an *ortho* substituent is also crucial, as 4-^{t}Bu-pyridine have been shown to be a reluctant substrate in the borylation reaction.[5]



Scheme 49. Selected borylation of pyridyl substrates.

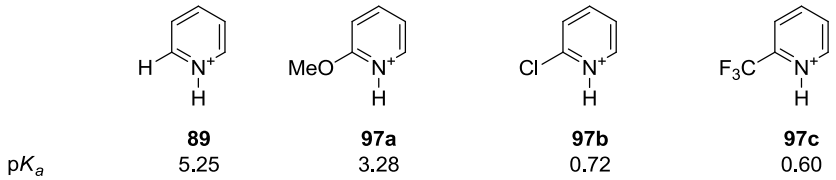
Although borylation alpha to a pyridyl nitrogen can be directed by sterics, the resultant α-pyridyl boronate ester derivatives (**95**) readily undergo protodeboronation.[4] Such decomposition is thought to proceed *via* an initial protonation of the pyridyl nitrogen followed by an alkoxide-assisted elimination of the boryl group leaving a negative charge on the adjacent carbon, which is then protonated (***Scheme 50***). The initial protonation step is crucial as direct elimination of the boryl group leads to the unfavourable formation of a high-energy intermediate **96**.



Scheme 50. Proposed mechanism for protodeboronation of α-pyridyl boronate esters.

This propensity for α-pyridyl boronic acids and their derivatives to undergo facile protodeboronation means that their use in cross-coupling reactions has been limited. Interestingly, however, David Blakemore at Neusentis, Pfizer, observed that unlike other pyridine derivatives, α-pyridyl boronate esters containing 2-OMe, 2-Cl or 2-CF_3 groups lead to unusually good conversions in Suzuki-Miyaura cross-coupling reactions. These results have not been published and were simply communicated to the author of this thesis and his supervisor, P. G. Steel, during a private discussion. Subsequent work by Blakemore and his team at Neusentis has since revealed that the pyridinium salt of the related 2-Cl, 2-OMe, and 2–CF_3 pyridines (**97a-c**) have significantly lower experimental pK_a values when compared to the parent pyridine molecule (***Figure 11***). These results suggests that these molecules are

less Lewis basic, which in turn, are less prone to protonation and the downstream protodeboronation process.



	89	**97a**	**97b**	**97c**
pK_a	5.25	3.28	0.72	0.60

Figure 11. Experimentally determined pK_a values for 2-Cl, 2-OMe and 2-CF_3 substituted pyridinium salts.

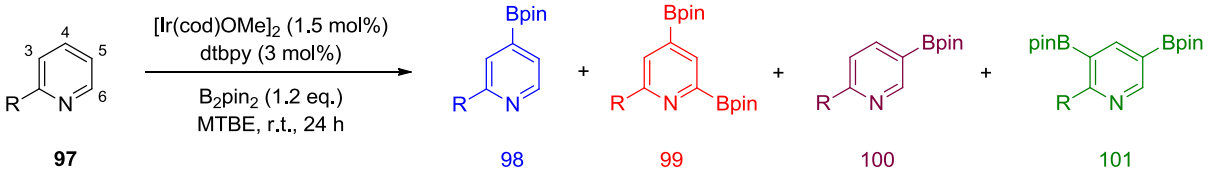
3.3 Chapter Goals

There is increased focus on reducing lipophilicity in drug discovery research. One way of achieving this is the replacement of non-polar aryl units with polar heterocyclic alternatives. Reflecting this, the synthesis of α-pyridyl boronate esters as precursors for Suzuki-Miyaura cross-coupling reactions is highly desirable. Iridium-catalysed aromatic C-H borylation could represent a convenient route to these compounds, provided the electronic barrier preventing the borylation alpha to the pyridyl nitrogen can be overcome. The subsequent section describes the borylation of a series of pyridine derivatives undertaken to determine the electronic and steric requirements for this reaction. The underlying hypothesis to this study is that the presence of an electron-withdrawing group at the 2-position of the pyridine nucleus would diminish the columbic repulsion responsible for the electronic barrier preventing the borylation of C-H bonds alpha to the pyridyl nitrogen.

3.4 Results and Discussion

3.4.1 Borylation of 2-Substituted Pyridines

Work in this area began with the borylation of simple 2-substituted pyridines. To account for the possibility that 6-borylated 2-substituted pyridines may be unstable to protodeboronation, the room-temperature borylation of these substrates (**97a-c**) were monitored *in-situ*. This involved charging a vial with the substrate under nitrogen followed by the addition of an aliquot of preformed stock solution containing $[Ir(cod)OMe]_2$ (1.5mol%), dtbpy (3 mol%) and B_2pin_2 (1.2 eq.) in MTBE. A 0.5 mL aliquot of this homogeneous solution was then transferred into an NMR tube fitted with a Young's tap containing a coaxial acetone-d_6 solvent stick and monitored by ^{1}H NMR spectroscopy. After 24 h, the reaction mixture was quenched with dichloromethane and concentrated. Analysis of this crude mixture and the reaction mixture after 24 h by ^{1}H NMR showed an identical mixture of products, suggesting that protodeboronation is not problematic. Full conversion of the starting arene materials was observed in all cases. Using a combination of ^{13}C NMR, COSY, HSQC and HMBC experiments, the products were identified as 4- and 5-borylated products as well as 3,5- and 4,6-bisborylated products (***Table 8***).



entry	97	R	^{1}H NMR ratio 98:99:100:101	*p* : *m* ratio (98+99):(100+101)
1	**a**	OMe	45 : 16 : 30 : 9	61 : 39
2	**b**	Cl	29 : 40 : 26 : 5	69 : 31
3	**c**	CF_3	20 : 42 : 38 : 0	62 : 38

Table 8. Borylation of 2-substituted pyridines at room temperature.

The lack of 2-borylated products in these reactions and the substantial formation of both 4-borylated and 4,6-bisborylated products suggests that product **99** arises from the second borylation of product **98**. Similarly, the absence of a 3-borylated product suggests that the bisborylated product **101** must form *via* a second borylation of monoborylated product **100**. Following these assumptions the underlying ratio of borylation at the 4- and 5-positions is approximately 7:3 for 2-chloro and 2-methoxy pyridines, with preferential borylation at the more deshielded 4-H (***Figure 12***). A similar regioselectivity was observed for 2-(trifluoromethyl) pyridine (**97c**). Although these regioselectivities are consistent with the C-H acidity hypothesis, the complete lack of borylation alpha to the pyridyl nitrogen in the absence of steric hindrance suggests that the electronic barrier preventing the activation of such C-H bond is large, even when the Lewis basicity of these substrates is relatively low.

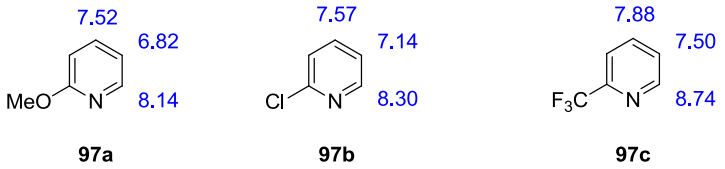
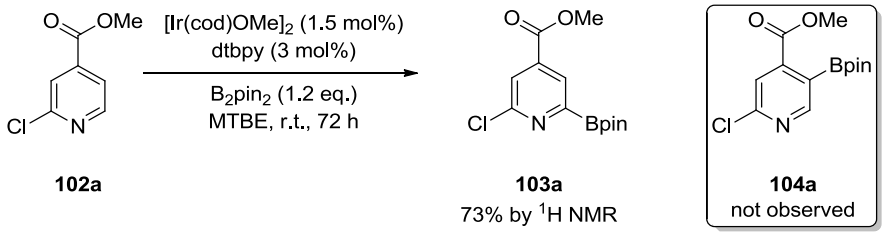


Figure 12. ^{1}H NMR chemical shifts of 2-substituted pyridines.

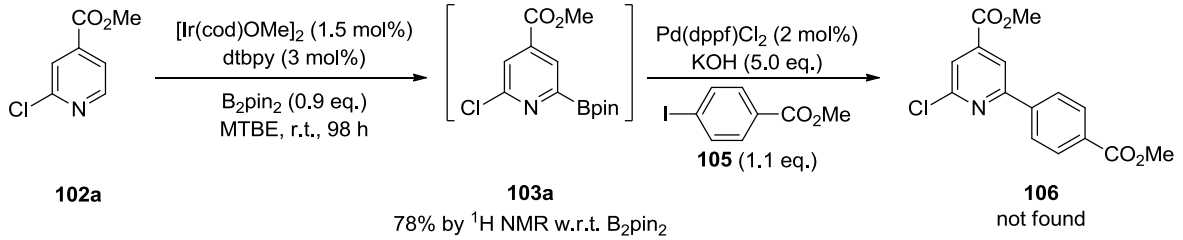
3.4.2 Borylation of Methyl 2-Chloroisonicotinate

Given the high electronic barrier preventing the borylation *ortho* to the pyridyl nitrogen, it was proposed that in an analogous fashion to the borylation of 4,4'-di-*tert*-butyl-2,2'-bipyridine, this can be overcome by steric effects. To this end, commercially available methyl 2-chloroisonicotinate (**102a**), was borylated under identical conditions as the 2-substituted pyridines above (***Scheme 51***). The formation of a single 6-borylated product (**103a**) could be clearly observed in the ^{1}H NMR spectrum of the reaction mixture *in-situ* as two fine doublets showing complementary coupling constants. After 72 h, the reaction reached a plateau at 73% conversion. Subsequent attempts to purify the product using flash column chromatography under a variety of solvent systems were undertaken. However, this proved challenging due to co-elution of residual B_2pin_2 and slow product degradation on the acidic silica column.



Scheme 51. Borylation of methyl 2-chloroisonicotinate.

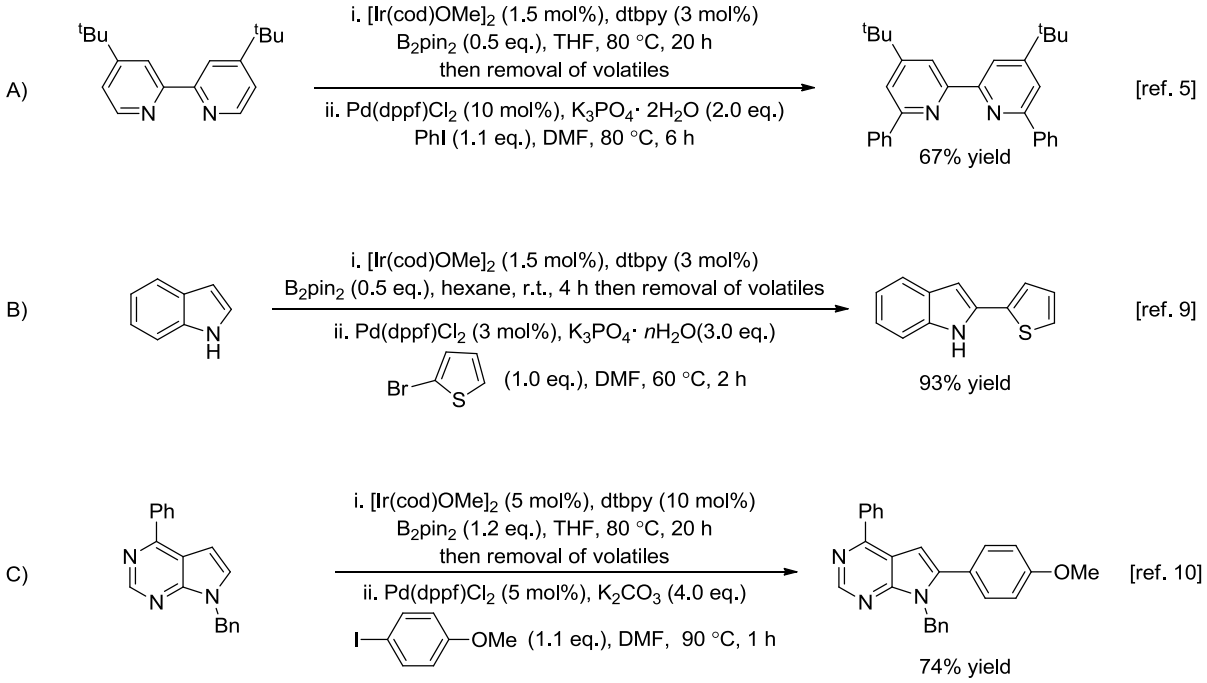
The borylation of **102a** was subsequently repeated with substoichiometric amounts of B_2pin_2 in the hope that a full consumption of the diboron reagent would lead to a less problematic purification (***Scheme 52***). Under these modified conditions however, a longer reaction time of 98 h was required and only 78% of the B_2pin_2 was converted (by ^{1}H NMR *in-situ*). Given this incomplete conversion, it was envisaged that a one-pot C-H borylation/Suzuki-Miyaura cross-coupling sequence previously developed in the group by Harrisson, could provide a viable alternative to the problematic purification of the borylated product.[4,6] This involved quenching of the borylation mixture with aq. KOH followed by the addition of 2 mol% $Pd(dppf)Cl_2$ and 1.1 equivalents of methyl 4-iodobenzoate (**105**). Following heating at 80 ˚C under microwave irradiation for 5 minutes however, only residual aryl halide (**105**) was recovered. It was thought that hydrolysis of the ester groups could have occurred leading to loss of materials on workup.



102a **103a** 78% by ^{1}H NMR w.r.t. B_2pin_2 **106** not found

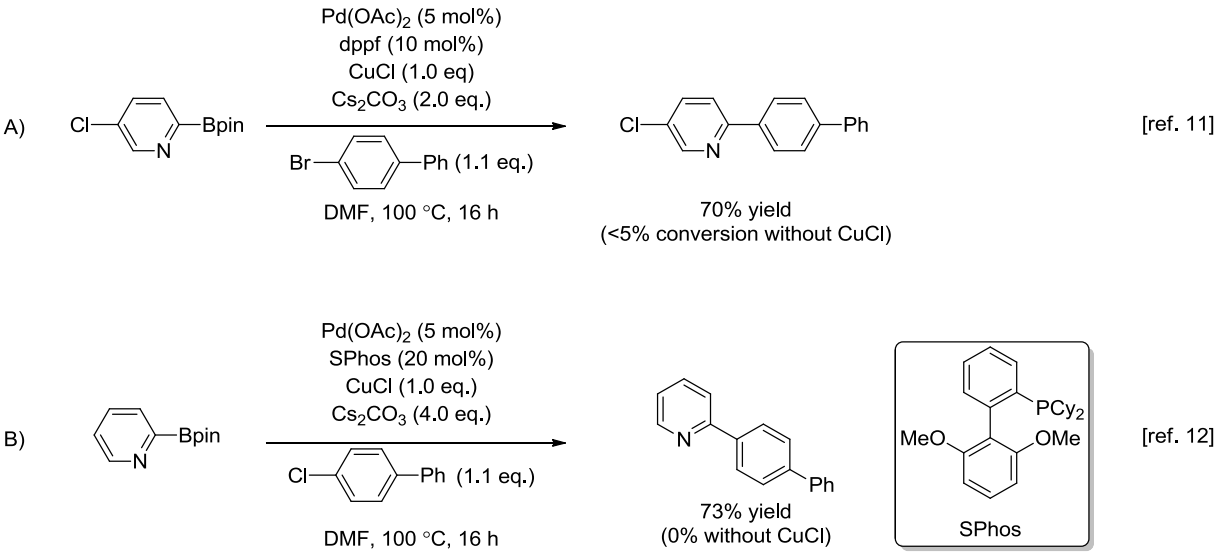
Scheme 52. Borylation of methyl 2-chloroisonicotinate using substoichiometric amounts of B_2pin_2.

With this in mind alternative protocols were considered. A brief survey of the literature revealed three other different Suzuki-Miyaura cross-coupling conditions developed specifically as a tandem sequence to the iridium-catalysed aromatic C-H borylation (***Scheme 53***).[5,9,10]



Scheme 53. C-H borylation/Suzuki-Miyaura cross coupling sequences in the literature.

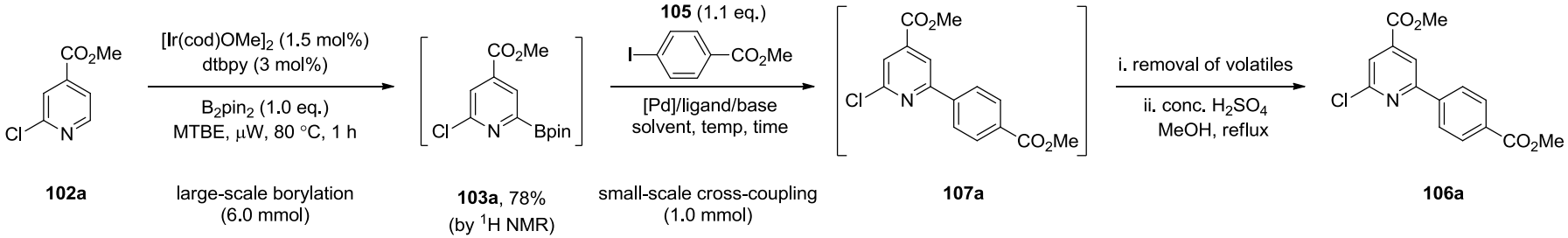
More recently, Burgey and co-workers have shown that Suzuki-Miyaura cross-coupling reactions in the presence of copper(I) chloride are particularly effective for the notoriously unstable 2-pyridyl boronate esters (***Scheme 54***).[11,12]



Scheme 54. Copper-assisted Suzuki-Miyaura cross-coupling reactions.

With these Suzuki Miyaura conditions noted, methyl 2-chloroisonicotinate (**102**) was borylated on a large 6.0 mmol scale using 15.0 mL of a preformed stock solution containing 3 mol% dtbpy, 1.5 mol% $[Ir(cod)OMe]_2$ and 1.0 equivalent B_2pin_2 (***Table 9***). Pleasingly, similarly high conversion of the pyridyl substrate (78%) compared to previous room temperature reactions was achieved under microwave heating after only 1 h (by ^1H NMR *in-situ*). A 2.5 mL aliquot of the reaction mixture was used to repeat Harrison's one-pot Suzuki-Miyaura cross-coupling protocol. The remaining mixture was concentrated, dissolved in DMF and then split into five equal portions. Each aliquot was transferred into to a crimp top microwave vial charged with appropriate amounts of the palladium catalyst, ligand, inorganic base, methyl

4-iodobenzoate, additional DMF and other required additives such as a drop of water or one equivalent of copper chloride. All six reactions were heated in parallel at the stated temperature and reaction times (***Table 9***). LC-MS analysis of the aqueous phase following aqueous workup of each reaction however, showed a large signal in the UV-trace exhibiting a single chlorine isotope pattern with peaks at *m*/*z* = 290 and 292, consistent with the hydrolysed biaryl product **107**. Such hydrolysis is unlikely to occur on the alkyl benzoate portion of the molecule given that these functionalities have been successfully used by Harrisson under this protocol before. The alkyl picolinate moiety however, is more electrophilic and is therefore more prone to hydrolysis. Nonetheless, following this observation, the aqueous phase was acidified to pH 5, extracted and combined with the organic phase from the initial aqueous work-up. These combined organic fractions were then concentrated and re-esterified using acidic methanol under reflux. Disappointingly, following the purification of the final biaryl units, low isolated yields (15-28%) were obtained for all six reactions.

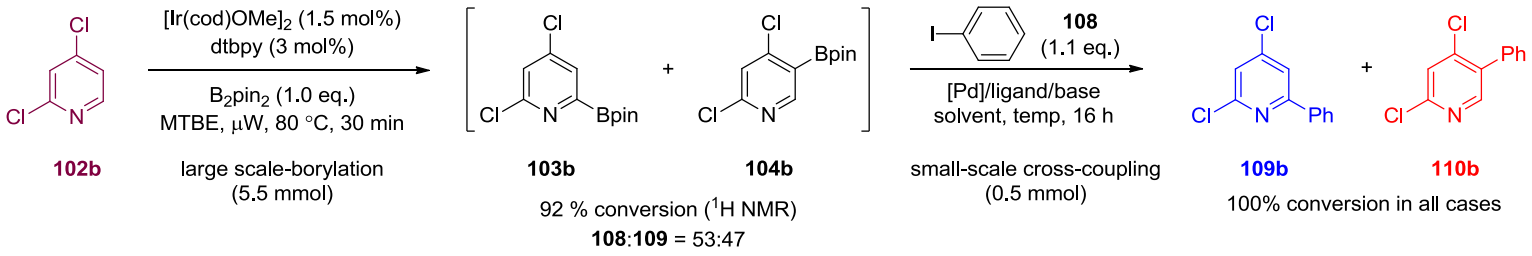


entry	removal of volatiles	[Pd] (mol%)	ligand (mol %)	base (eq.)	other additives	solvent (mL)	temp. (˚C)	time (h)	isolated yield **106a**	ref.
1	✗	$Pd(dppf)Cl_2$ (3)	-	KOH (5.0)	-	H_2O (0.4)	80	5min	15%	[8]
2	✓	$Pd(dppf)Cl_2$ (3)	-	K_3PO_4 (3.0)	-	DMF (1.6)	60	2	28%	[9]
3	✓	$Pd(dppf)Cl_2$ (5)	-	K_2CO_3 (4.0)	H_2O (3 drops)	DMF (1.6)	90	10	38%	[10]
4	✓	$Pd(dppf)Cl_2$ (10)	-	K_3PO_4 (2.0)	-	DMF (4.0)	80	6	28%	[5]
5	✓	$Pd(OAc)_2$ (5)	dppf (10)	Cs_2CO_3 (2.0)	CuCl (1.0 eq.)	DMF (4.0)	100	16	23%	[11]
6	✓	$Pd(OAc)_2$ (5)	Sphos (20)	Cs_2CO_3 (4.0)	CuCl (1.0 eq.)	DMF (4.0)	100	2	15%	[12]

Table 9. Screening of Suzuki-Miyaura cross-coupling conditions on methyl 2-chloroisonicotinate crude borylation mixture.

3.4.3 Borylation of 2,4-Dichloropyridine

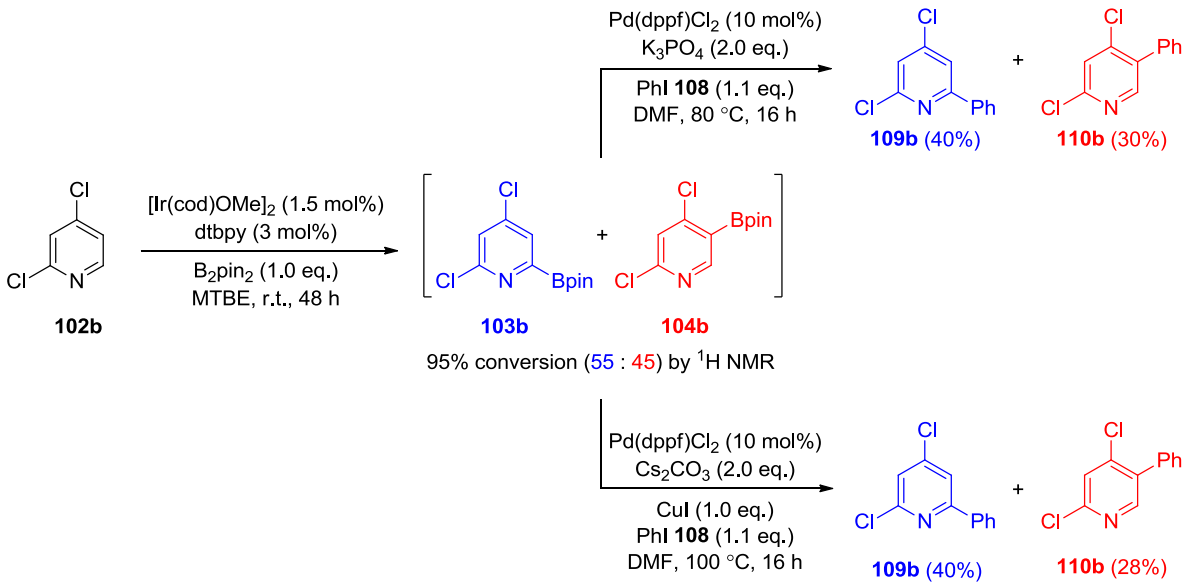
Given the problematic side-reaction of an alkyl picolinate group, the more hydrolytically stable 2,4-dichloropyridine (**102b**) was explored as an alternative substrate (***Table 10***). Unlike methyl 2-chloroisonicotinate (**102a**) however, the reaction of 2,4-dichloropyridine proceeded with significant borylation at C-5, reflecting the smaller steric demand of the chlorine atom compared with a methyl ester. The formation of 5-borylated product **104b**, could clearly be ascertained by the appearance of two singlets in the ^{1}H NMR spectrum of the reaction mixture. In a similar fashion to the previous screening of Suzuki-Miyaura cross-coupling conditions, the reaction mixture was split into equal portions for the subsequent cross-coupling reactions, this time using iodobenzene (**108**) rather than methyl 4-iodobenzoate (**105**) to avoid the possibility of ester hydrolysis. Unlike the previous screening however, with the exception of the Harrisson protocol (***Table 10***, entry 1), each set of conditions was employed under both 'one-pot' conditions (without removal of volatiles) and as two distinct steps. Pleasingly, good yields of both biaryl products **109b** and **110b** were obtained as a mixture for most of these reactions. The cross-coupling reactions in entries 4, 10 and 11 were unsuccessful, presumably due to practical errors. Since some of the remaining protocols appeared to be effective, these reactions were not repeated in the interest of time.



entry	solvent removal	[Pd] (mol%)	ligand (mol%)	base (eq.)	additives	solvent (mL)	temp. (˚C)	102b (%)	109b:110b ratio GC-MS	109b:110b ratio ^{1}H NMR	combined yield (%)
1	×	$Pd(dppf)Cl_2$ (3)	-	KOH (5.0)	-	H_2O (0.4)	80 (μW)	8	48:52	50:50	51
2	✓	$Pd(dppf)Cl_2$ (3)	-	K_3PO_4 (3.0)	-	DMF (1.6)	60	12	41:59	37:63	66
3	×	$Pd(dppf)Cl_2$ (3)	-	K_3PO_4 (3.0)	-	DMF (1.6)	60	18	49:51	48:52	59
4	✓	$Pd(dppf)Cl_2$ (5)	-	K_2CO_3 (4.0)	H_2O (3 drops)	DMF (1.6)	90	100	-	-	-
5	×	$Pd(dppf)Cl_2$ (5)	-	K_2CO_3 (4.0)	H_2O (3 drops)	DMF (1.6)	90	12	50:50	50:50	68
6	✓	$Pd(dppf)Cl_2$ (10)	-	K_3PO_4 (2.0)	-	DMF (4.0)	80	4	42:58	47:53	43
7	×	$Pd(dppf)Cl_2$ (10)	-	K_3PO_4 (2.0)	-	DMF (4.0)	80	5	48:52	52:48	64
8	✓	$Pd(OAc)_2$ (5)	dppf (10)	Cs_2CO_3 (2.0)	CuCl (1.0 eq.)	DMF (4.0)	100	0	64:36	64:36	66
9	×	$Pd(OAc)_2$ (5)	dppf (10)	Cs_2CO_3 (2.0)	CuCl (1.0 eq.)	DMF (4.0)	100	7	58:42	61:39	67
10	✓	$Pd(OAc)_2$ (5)	Sphos (20)	Cs_2CO_3 (4.0)	CuCl (1.0 (eq.)	DMF (4.0)	100	100	-	-	-
11	×	$Pd(OAc)_2$ (5)	Sphos (20)	Cs_2CO_3 (4.0)	CuCl (1.0 eq.)	DMF (4.0)	100	100	-	-	-

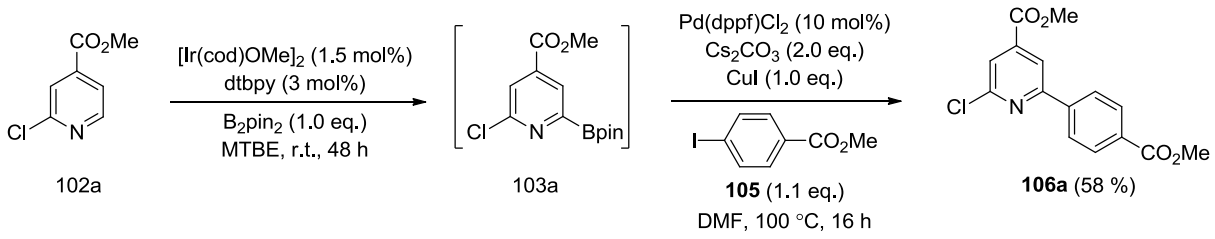
Table 10. Screening of Suzuki-Miyaura cross-coupling conditions on 2,4-dichloropyridine crude borylation mixture.

Although the conditions outlined in entries 2, 3, 5, 7, 8 and 9 all gave similarly high yields, the low base loading requirement, the one-pot method and the low levels of protodeboronation in entries 7 and 8 are all particularly outstanding traits. A subsequent repeat of these two selected conditions on a larger 2.0 mmol scale afforded almost identical results (***Scheme 55***).



Scheme 55. C-H borylation/Suzuki-Miyauara cross-coupling sequence on 2,4-dichloropyridine.

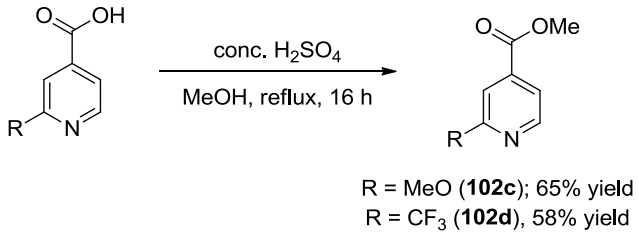
Pleasingly, application of the sequence involving CuI in the Suzuki-Miyaura cross-coupling step on methyl 2-chloroisonicotinate (**102a**) and methyl 4-iodobenzoate (**105**) afforded the biaryl **106a** in 58% yield (***Scheme 56***).



Scheme 56. C-H borylation/Suzuki-Miyaura cross-coupling sequence on methyl 2-chloroisonicotinate.

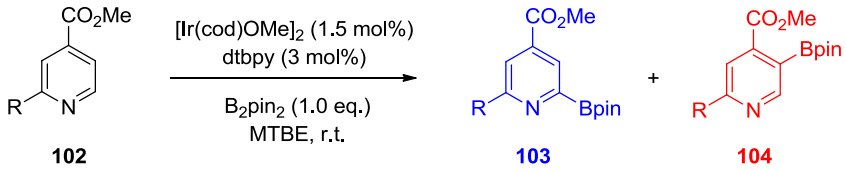
3.4.4 Borylation of 2-Cl-, 2-OMe-, and 2–CF_3 4-substituted Pyridines

Having identified effective sequential C-H Borylation/Suzuki-Miyaura cross-coupling conditions, a series of 2,4-disubstituted pyridines were considered for borylation. Although alkyl picolinate functional groups have been shown to be particularly sensitive to hydrolysis, methyl 2-methoxyisonicotinate (**102c**) and methyl 2-(trifluoromethyl)isonicotinate (**102d**) can be readily obtained from methylation of the corresponding carboxylic acids, both of which are commercially available (***Scheme 57***).



Scheme 57. Synthesis of methyl 2-methoxyisonicotinate and methyl 2-(trifluoromethyl)isonicotinate.

Subsequent borylation of these substrates as well as methyl 2-chloroisonicotinate (**102a**), afforded almost exclusively 6-borylated products **103a**, **103c**, and **103d** by ^{1}H NMR spectrum *in-situ* of the reaction mixture (***Table 11***). The lack of 5-borylated products is reminiscent of the reported borylation of dtbpy, which is attributed to the large steric demand of the ester groups.

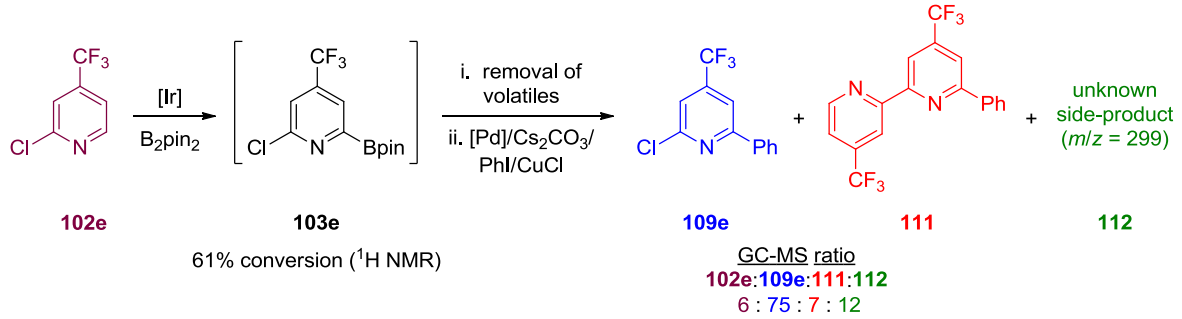


102 **103** **104**

entry	**102**	R	time (h)	conv. (%)	**103** : **104**
1	**a**	Cl	72	78	100 : 0
2	**c**	OMe	24	57	100 : 0
3	**d**	CF_3	1	93	93 : 7

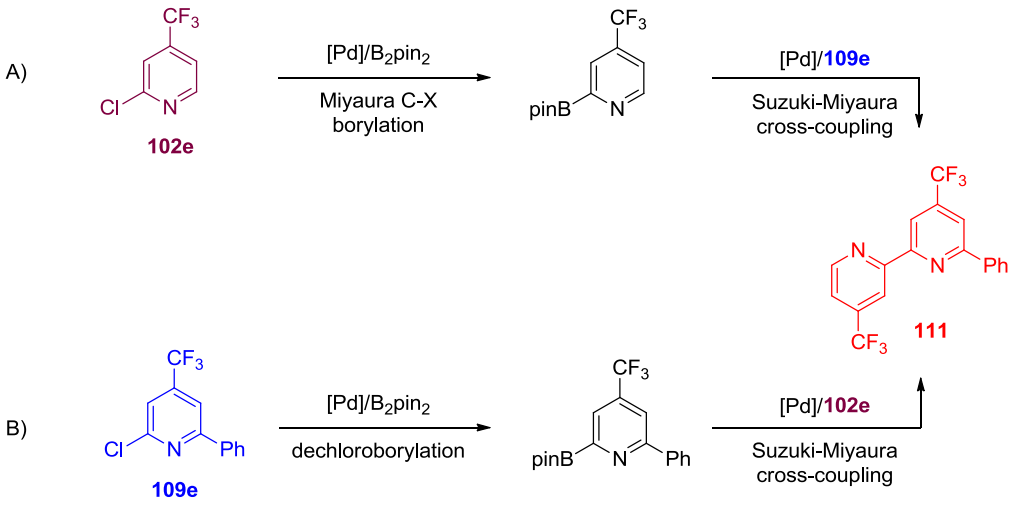
Table 11. Borylation of methyl 2-substituted isonicotinates.

Borylation of the analogous 2-chloro-4-trifluoromethyl pyridine (**102e**), also leads to formation of the 6-borylated product. However, significant amounts of side-products were detected by GC-MS following the subsequent Suzuki-Miyaura cross-coupling step (***Scheme 58***). While the formation of bipyridyl **111** could be identified from a peak exhibiting a lack of chlorine isotope pattern with *m*/*z* = 368, the remaining side-product **112** with *m*/*z* = 232 was not identifiable.



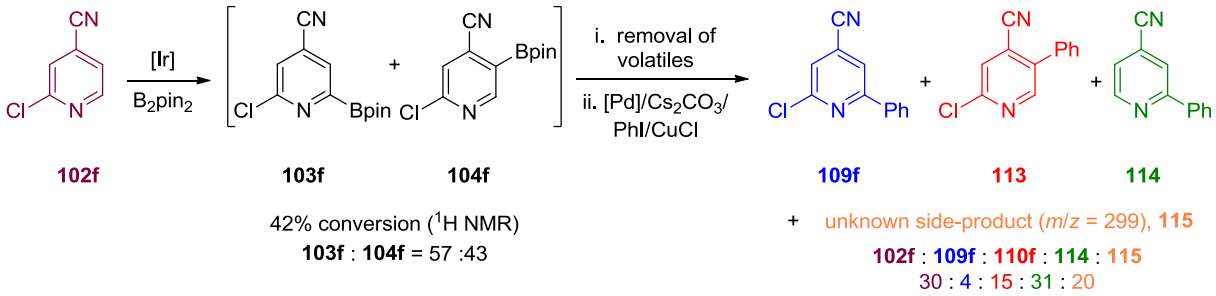
Scheme 58. C-H borylation/Suzuki-Miyaura cross-coupling sequence on 2-chloro-4-(trifluoromethyl)pyridine.

The formation of **111** could be explained by an initial reaction between the residual **102e** and B_2pin_2 in the presence of a palladium catalyst followed by a Suzuki-Miyaura cross-coupling reaction of the resultant boronate ester with **109e** (***Scheme 59A***). This could account for the substantial reduction in the amounts of **102e** following the Suzuki-Miyaura cross-coupling step. Alternatively, in the presence of residual B_2pin_2, **109e** undergoes dechloroborylation at C-2 followed by a Suzuki-Miyaura cross-coupling with residual **102e** (***Scheme 59B***).



Scheme 59. Possible routes to the bipyridyl side-product.

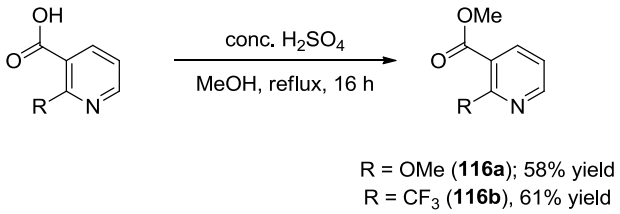
An attempt to subject this sequence to 2-chloro-4-cyano pyridine (**109f**) also afforded a complex mixture of products (***Scheme 60***). Careful GC-MS analysis of the crude reaction mixture revealed significant formation of **114** (presumably through protodechlorination of **102f**), identified by a peak at *m*/*z* = 180 and a lack of chlorine isotope pattern. Unfortunately, the remaining side-product exhibiting a peak at *m*/*z* = 299 was not identifiable.



Scheme 60. C-H borylation/Suzuki-Miyaura cross-coupling sequence on 2-chloro-4-cyanopyridine.

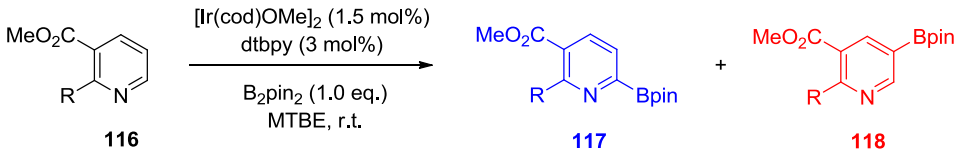
3.4.5 Borylation of Methyl 2-Substituted Nicotinates

It is clear from the borylation of 2-substituted and 2,4-disubstituted pyridines that extreme steric effects are required to selectively direct borylation alpha to the pyridyl nitrogen. On this basis, it was proposed that steric blocking of the 4-position in 2,3-disubstituted pyridines should lead to exclusive borylation at the 5-position, leaving H-6 completely intact. To investigate this, methyl 2-methoxy nicotinate (**16a**), and methyl 2-(trifluoromethyl)nicotinate (**16b**) were prepared through the methylation of the corresponding commercially available carboxylic acids (***Scheme 61***).



Scheme 61. Synthesis of methyl 2-methoxynicotinate and methyl 2-(trifluoromethyl)nicotinate.

Consistent with the above hypothesis, subsequent borylation of these substrates, as well as the commercially available methyl 2-chloronicotinate (**116c**), afforded 5-borylated products **118a-c** almost exclusively.



entry	**116**	R	time (h)	conv. (%)	**117** : **118**
1	**a**	Cl	45	78	6 : 94
2	**b**	OMe	25	100	7 : 93
3	**c**	CF_3	1	100	0 : 100

Table 12. C-H borylation/Suzuki-Miyaura cross-coupling sequence on methyl 2-substituted nicotinates.

3.5 Conclusions

The regioselectivity of the iridium-catalysed aromatic C-H borylation is contingent on C-H acidity in the absence of steric effects. The borylation of C-H bonds alpha to the nitrogen atom in pyridine derivatives however, is inhibited by an electronic barrier arising from a coulombic repulsion between the pyridyl nitrogen lone pair and the formation of a partial negative charge on the adjacent carbon during C-H activation. In the studies described above, attempts to sequester the Lewis basicity of the pyridyl lone pair by introducing electron-withdrawing groups at the 2-position of pyridine derivatives were not successful. This inhibitory electronic effect however, can be overcome by introducing extremely large steric groups such as CF_3 and CO_2Me at the 4-position. Smaller substituents such as Cl and CN lead to a mixture of 5- and 6-borylated products demonstrating the high electronic barrier involved in activating C-H bonds alpha to a pyridyl nitrogen. A one-pot C-H borylation/Suzuki-Miyaura cross-coupling sequence has also been developed to enable the purification of the biaryl unit derived from the notoriously unstable α-pyridyl boronate esters formed initially in the borylation step.

3.6 References

[1] Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.

[2] Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3.

[3] Vanchura, I. I. B. A.; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, J. R. E.; Singleton, D. A.; Smith, I. I. I. M. R. *J. Chem. Soc., Chem. Commun.* **2010**, *46*, 7724.

[4] Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586.

[5] Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489.

[6] Thorpe, S. B.; Calderone, J. A.; Santos, W. L. *Org. Lett*. **2012**, *14*, 1918

[7] Nguyen, P.; Dai, C.; Taylor, N. J.; Power, W. P.; Marder, T. B. *Inorg. Chem.* **1995**, *34*, 4290

[8] Harrisson, P.; Morris, J.; Steel, P. G.; Marder, T. B. *Synlett* **2009**, 147.

[9] Kikuchi, T.; Nobuta, Y.; Umeda, J.; Yamamoto, Y.; Ishiyama, T.; Miyaura, N. *Tetrahedron* **2008**, *64*, 4967.

[10] Klecka, M.; Pohl, R.; Klepetarova, B.; Hocek, M. *Org. Biomol. Chem.* **2009**, *7*, 866.

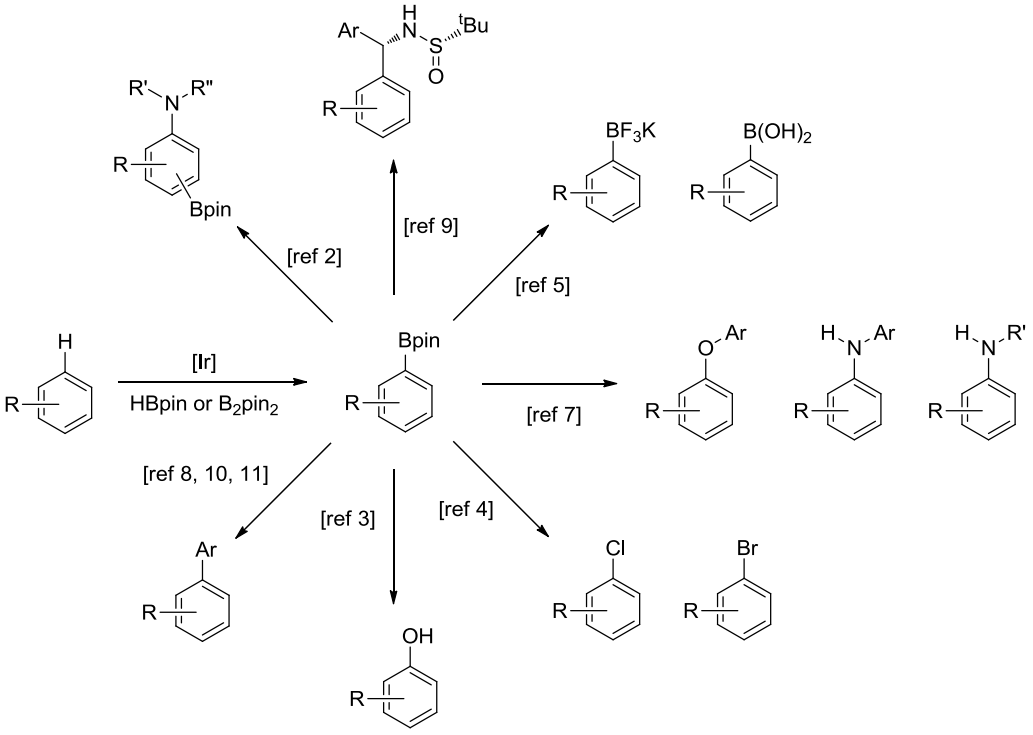
[11] Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345.

[12] Crowley, B. M.; Potteiger, C. M.; Deng, J. Z.; Prier, C. K.; Paone, D. V.; Burgey, C. S. *Tetrahedron Lett.* **2011**, *52*, 5055.

Chapter 4 - “One-Pot” Tandem Ir-Catalysed Aromatic C-H Borylation/Rh-Catalysed 1,4-Conjugate Addition Sequence

4.1 Aims and Objectives

The use of combinatorial or array chemistry to build chemical libraries for rapid exploration of structure-activity relationships is an important strategy to enhance drug discovery.[1] Effective protocols typically need to be robust and efficient under generalised reaction conditions across a wide range of substrate structures. As seen in chapters 1 and 2, the direct borylation of aromatic C-H bonds promoted by iridium trisboryl complexes has developed into a popular and powerful method for the functionalisation of arenes. This transformation is ideally suited to array chemistry as it avoids the need for specifically functionalised precursors and exploits the diverse chemistry of the resulting boronate ester. This is most effective when carried out in a single vessel, and such *in-situ* elaboration of the initially formed boronate ester can provide rapid access to a variety of functionalized arenes (*Scheme 62*).[2-9] One example of this is Harrisson's report on the use of MTBE as a compatible solvent for both the borylation and the Suzuki-Miyaura cross-coupling reactions and showing that both processes can be efficiently accelerated using microwave irradiation.[10,11] To build on this work, and to further contribute to this 'one-pot' methodological toolbox, the subsequent section describe efforts directed at exploring rhodium-catalysed 1,4-conjugate addition for the *in-situ* elaboration of aryl boronate esters to form a library of β-aryl carbonyl compounds.



Scheme 62. Literature examples of "one-pot" elaboration of arylboronate esters formed in iridium-catalysed C-H borylation.

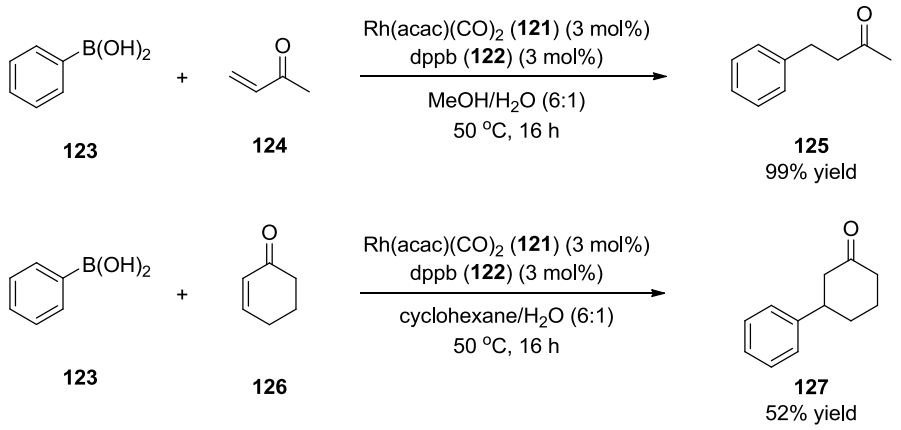
4.2 Rhodium-Catalysed 1,4-Conjugate Addition of Organoboranes

Carbon-carbon bond formation is a fundamentally important tool in synthetic organic chemistry. In particular, rhodium-catalysed 1,4-conjugate addition of organoboron compounds is a valuable method for the concomitant construction of new stereogenic centres through the use of chiral catalysts.[12,13] Since its discovery, considerable advances in this area over the last 20 years has led to the ability for these reactions to be undertaken with high efficiency and stereoselectivity. Consequently, it has become the method of choice for C(sp^2) nucleophiles, complementing the related copper methodology that employs hard organometallic C(sp^3) nucleophiles such as organolithium,[14,15] -magnesium,[16-18] or –zinc reagents.[19-22] The following section presents an overview of the scope and key advances made in the rhodium-catalysed 1,4-conjugate addition methodology. For a more comprehensive review, see references 12 and 13.

4.2.1 Discovery of the Rhodium-Catalysed 1,4-Conjugate Addition Reaction and Key Advances

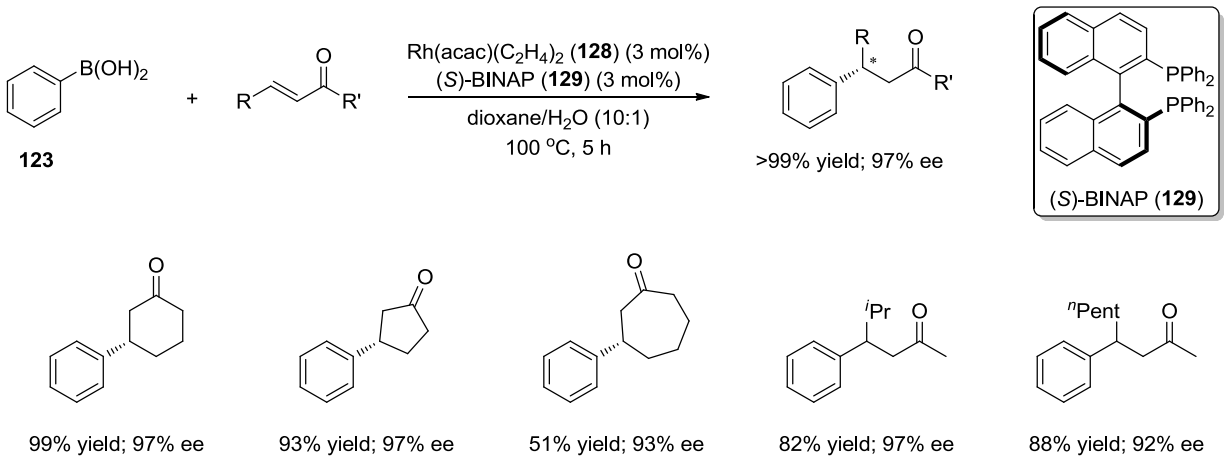
The use of rhodium(I) complexes to catalyse the 1,4-conjugate addition of aryl and alkenyl boronic acids to enones was first reported in 1997 by Miyaura and co-workers (***Scheme 63***).[23] By using Rh(acac)$(CO)_2$ (**121**) as a catalyst precursor, it was noted that water and a bis(phosphine) ligand possessing large bite angles such as bis(diphenylphosphino)butane (dppb) (**122**) were required for good reactivity. However, while products arising from conjugate addition to β-unsubstituted enones such as methylvinylketone (MVK) (**124**) were

obtained in high yields, β-substituted enones such as cyclohex-2-enone (**126**) were much less reactive resulting in poor yields.



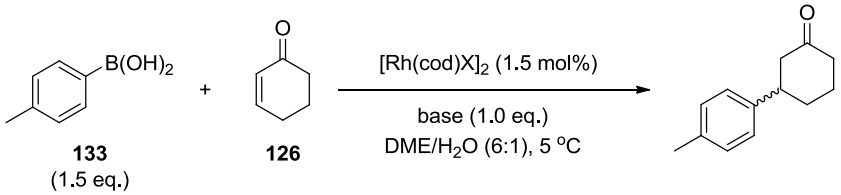
Scheme 63. First reported rhodium-catalysed 1,4-conjugate addition of organoboranes.

Subsequently, Hayashi and Miyaura showed that additions to cyclic and linear β-substituted enones can be carried out with improved efficiency as well as excellent enantioselectivity by switching to a catalyst generated from $Rh(acac)(C_2H_4)_2$ (**128**) and the chiral phosphine ligand BINAP (**129**) and employing a high excess of the boronic acids (up to 5.0 equivalents) to account for the competing protodeboronation side-reaction (***Scheme 64***).[24] This reaction has since become a benchmark for subsequent work in rhodium-catalysed 1,4-conjugate addition of organoboranes both in terms of reactivity and enantioselectivity.



Scheme 64. First reported asymmetric rhodium-catalysed 1,4-conjugate addition.

Although Rh(acac)$(C_2H_4)_2$ (**128**) has since been widely used with good success, rhodium sources possessing a cyclooctadiene ligand such as [Rh(cod)Cl]$_2$ (**130**),[25] Rh(cod)OH]$_2$ (**131**),[25] and [Rh(cod)$_2$][PF_6] (**132**)[26] have recently been shown to be more effective. Key to the high reactivity of these systems is the weak binding between the rhodium and the diene ligand, shifting the equilibrium towards the catalytically active hydroxo-rhodium species in the presence of water (more on this in section 4.2.2). Consistent with this, the conjugate addition of *p*-tolylboronic acid (**133**) to cyclohex-2-enone (**126**) at 5 ˚C using [Rh(cod)Cl]$_2$ (**130**) in the absence of base is slower than the analogous reaction employing the corresponding rhodium-hydroxo complex, [Rh(cod)OH]$_2$ (**131**) (***Figure 13***). Moreover, a remarkable acceleration effect can be obtained through the addition of an inorganic base, such as KOH, particularly at low temperature.[25] The addition of base presumably aids the generation of the rhodium-hydroxo species.



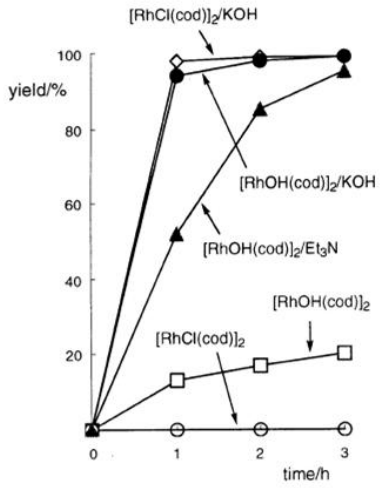
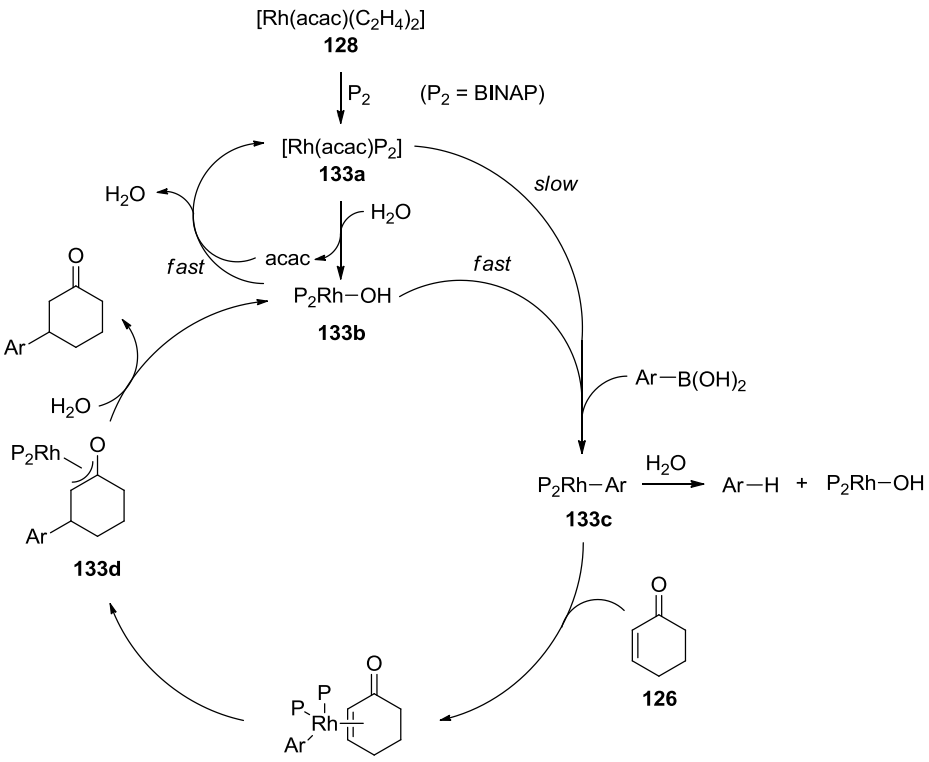


Figure 13. $[Rh(cod)Cl]_2$ *versus* $[Rh(cod)OH]_2$ and accelerating effect of bases on rhodium-catalysed 1,4-conjugate addition of *p*-tolyboronic acid to cyclohex-2-enone.

4.2.2 Proposed Catalytic Cycle

Detailed mechanistic studies on the rhodium-catalysed 1,4-conjugate addition of arylboronic acids to enones were reported by Hayashi in 2002.[27] On the basis of NMR studies, the catalytic cycle was proposed to proceed *via* three key intermediates, arylrhodium **133c**, oxa-π-allylrhodium **133d** and hydroxorhodium **133b** complexes (***Scheme 65***).[27] With $[Rh(acac)(C_2H_4)_2]$ (**128**) as a catalyst precursor, the hydroxorhodium species **133b** was formed through an initial ligation of added phosphine ligands accompanied by a loss of ethene gas. In the presence of water, the resultant complex exists in equilibrium with the catalytically active **133b**. Although the transmetalation of the arylboronic acid to form

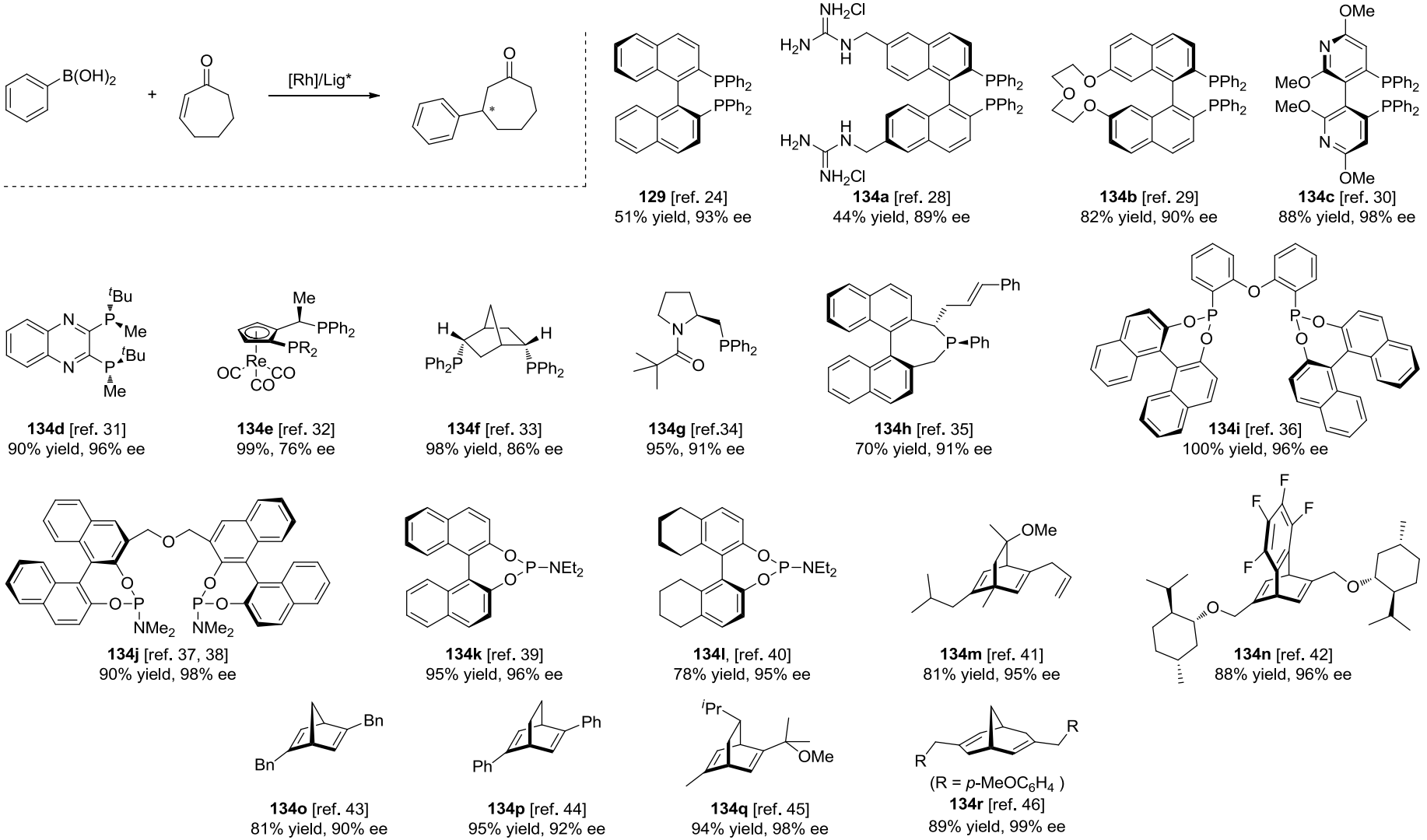
arylrhodium complex **133c** can occur directly with **133a**, this process is very slow and occurs more readily for **133b**. Two pathways are possible at this stage; the arylrhodium complex **133c** can either undergo hydrolysis in a competing side-reaction or it can coordinate with the alkene and then undergo arylrhodation to the oxa-π-allylrhodium complex **133d**. Protonolysis of this complex releases the conjugate addition product, regenerates **133b** and triggers the reversible formation of the rhodium-acac complex **133a**. In presence of a base such as KOH, this equilibrium is shifted to the more reactive hydroxorhodium species **133b** leading to faster reaction rates.



Scheme 65. Proposed catalytic cycle for rhodium-catalysed 1,4-conjugate addition of arylboronic acid to cyclohex-2-enone.

4.2.3 Chiral Ligands

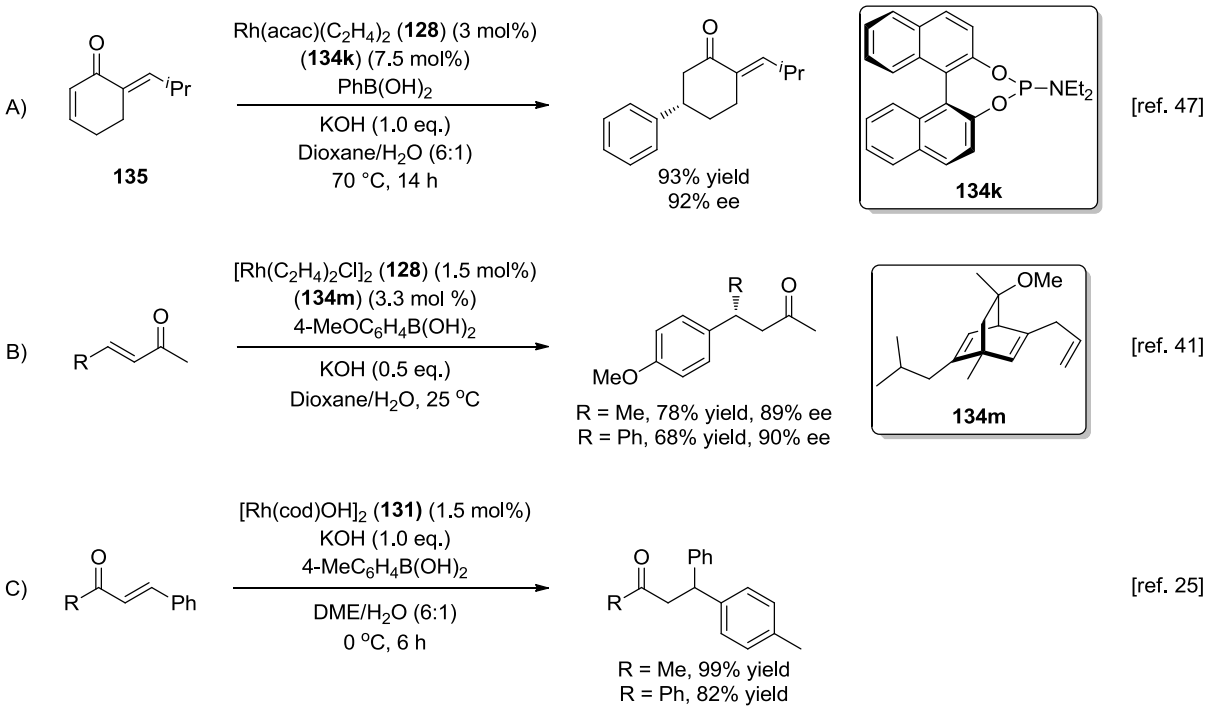
Since Hayashi and Miyaura's report on the first enantioselective rhodium-catalysed 1,4-conjugate addition, a large variety of chiral ligands have been explored (***Scheme 66***). Like BINAP, the use of a binaphthyl backbone such as in **134a**[28] and **134b**[29] leads to high levels of enantioselectivity, with significantly higher reactivity observed in using the latter. Bipyridyl atropisomeric diphosphines (**134c**)[30] exhibit markedly superior reactivity and enantioselectivity, as does a P-chiral diphosphine ligand (**134d**).[31] Superior reactivity can be achieved with the related cyrhetrene (**134e**)[32] and diphonane (**134f**)[33] derivatives but at the expense of enantioselectivity. Away from chiral diphosphines, some success has been found with hemilabile ligands such as amidophosphines (**134g**)[34] and alkenophosphines (**134h**)[35] while generally excellent yields and enantioselectivity were found with a bisphosphonite (**134i**)[36] and phosphoramadite ligands such as **134j-l**.[37-40] This reactivity and enantioselectivity is closely rivalled by a range of chiral dienes based on a bicyclic skeleton (**134m-r**).[41-46]



Scheme 66. Examples of chiral ligands in rhodium-catalysed 1,4-conjugate addition reactions.

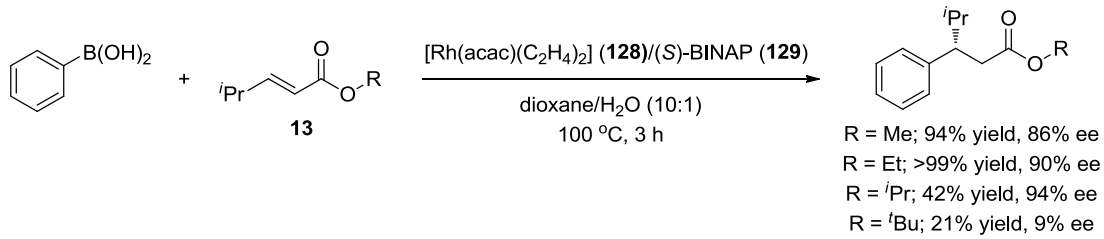
4.2.4 Acceptors

In rhodium-catalysed 1,4-conjugate addition, α,β-unsaturated ketones are the most reactive and commonly used class of acceptors. Generally, simple unsubstituted enones are more reactive than the sterically more demanding substrates. For example, MVK (**124**) readily undergoes the addition process under Hayashi and Miyaura's original conditions.[23] However, cyclohex-2-enone (**126**) require the use of more efficient catalysts derived for example from $Rh(acac)(C_2H_4)_2$ (**128**).[24] Consistent with this steric effect, cyclic β-substituted enones are more reactive than the analogous acyclic variant. For example, Krause and co-workers showed that 1,4-conjugate addition proceed chemoselectively at the endocyclic C-C double bond in a bifunctional Michael acceptor **135** containing a trisubstituted exocyclic alkene moiety (***Scheme 67A***).[47] Moreover, β-arylsubstituted enones are less reactive than β-alkyl substituted enones (***Scheme 67B***).[41] Similarly, but not surprisingly, aryl vinyl ketones are less reactive than their aliphatic counterparts (***Scheme 67C***).[25]



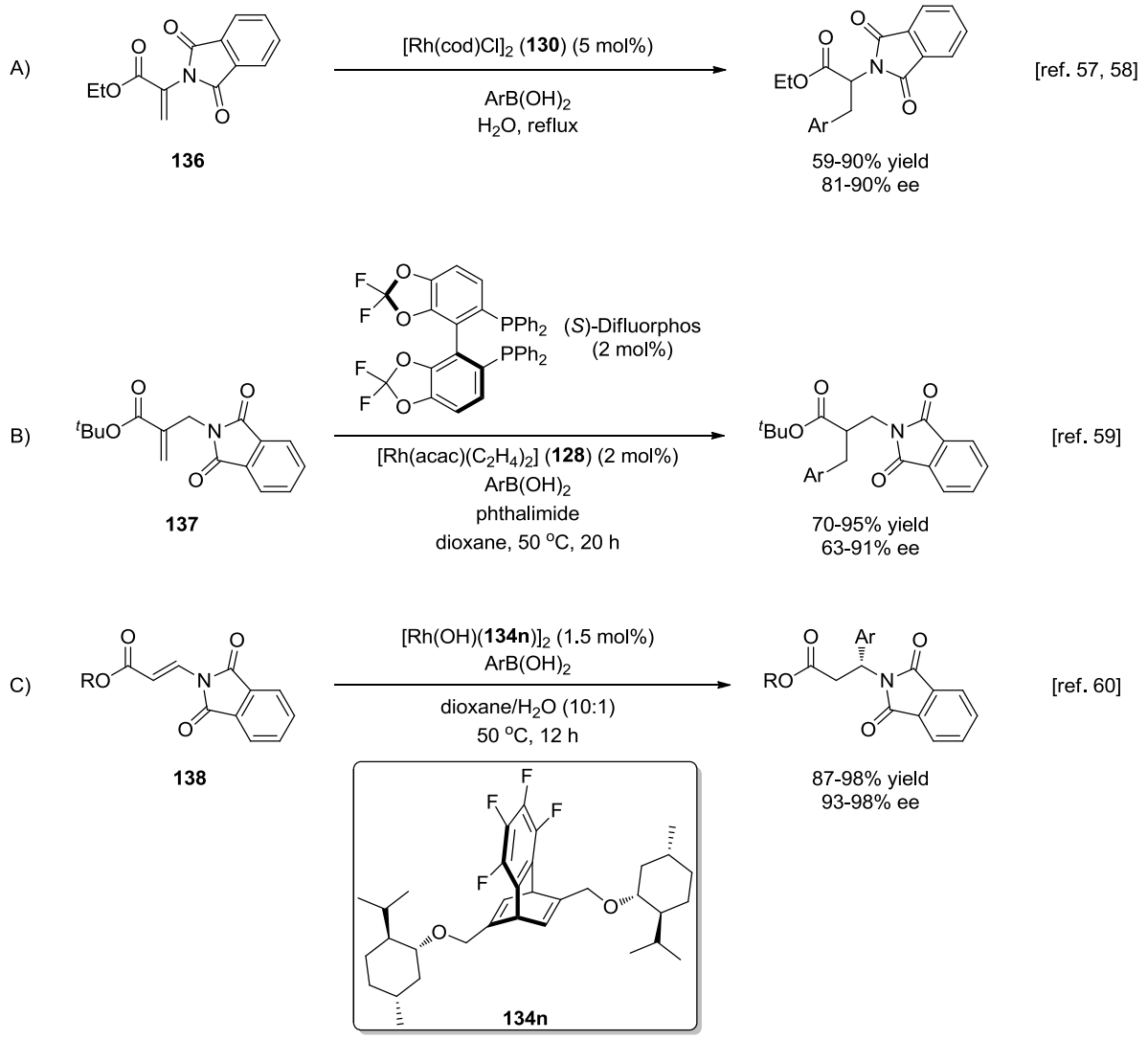
Scheme 67. Steric effects on the reactivity of substituted enones in 1,4-conjugate addition.

After enones, α,β-unsaturated esters are the second most commonly used class of acceptors in rhodium-catalysed 1,4-conjugate addition. Enoates are generally less reactive than enones, and like their more reactive counterpart, steric effects have a profound influence on reactivity. Hayashi and co-workers showed that reactivity decreases with increasing steric bulk of the ester moiety (***Scheme 68***).[48]



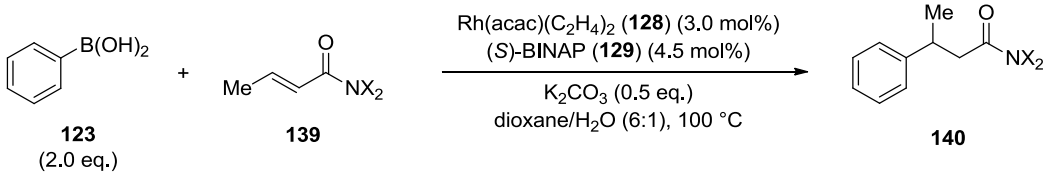
Scheme 68. Steric effects on the reactivity of enoates in 1,4-conjugate addition.

A large range of enoates have been successfully employed in this 1,4-conjugate addition methodology including β-aryl acrylates,[49] β-aryl-α-cyano acrylates,[50] β-benzyl acrylates,[51] α,β-unsaturated N-protected-3-aziridines,[52] fumaric esters,[53] 2,4-dienoate esters,[54] coumarins[55] and chiral δ-hydroxy-γ-butenolides[56] as acceptors. However, α,β-unsaturated esters possessing β-substituted amine functionality give poor yields unless the amine group is masked as phthalimide. These substrates are particularly useful for the synthesis of a wide variety of functionalised amino acids. Examples of this include the 1,4-addition to α,β-dehydroamino acid derivatives (**136**),[57,58] α-methylamino acrylates (**137**)[59] and β-phthalimino acrylates (**138**)[60] providing general synthesis of α-, β^2- and β^1-amino acid derivatives respectively (***Scheme 69***).



Scheme 69. Synthesis of functionalized amino acids using rhodium-catalysed 1,4-conjugate addition reactions.

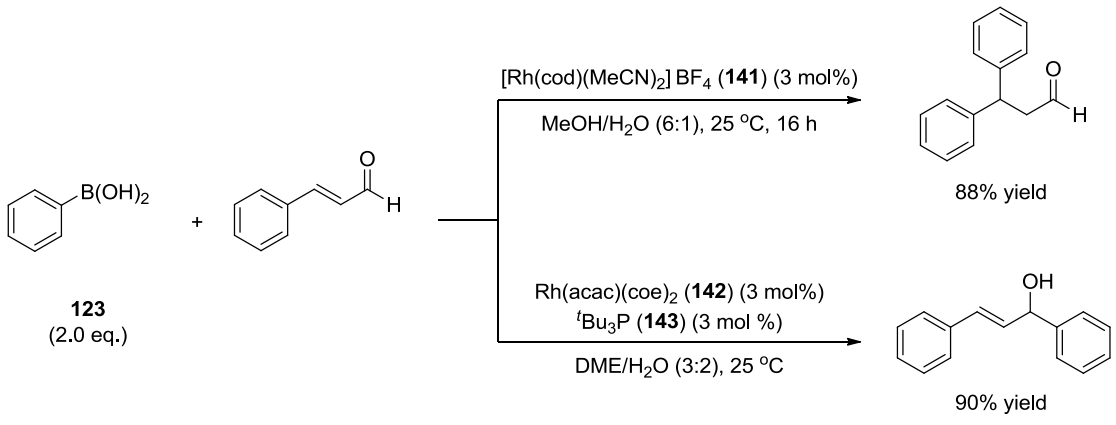
α,β-Unsaturated amides are less reactive when compared to the corresponding enones and enoates. Miyaura and co-workers showed that while crotonamide (**139a**) proceeded smoothly in 1,4-conjugate addition (***Table 13***, entry 1), better reactivity was observed with both N-aryl and N-alkylsubstituted crotonamides (***Table 13***, entries 2 and 3). However, consistent with the steric effects observed with enoates, the presence of another substituent at the amido nitrogen diminishes reactivity (***Table 13***, entry 4).



entry	**139**	NX_2	yield **140** (%)	ee (%)
1	**a**	NH_2	62	89
2	**b**	N(H)cy	80	93
3	**c**	N(H)Ph	88	90
4	**d**	piperidine	no reaction	-

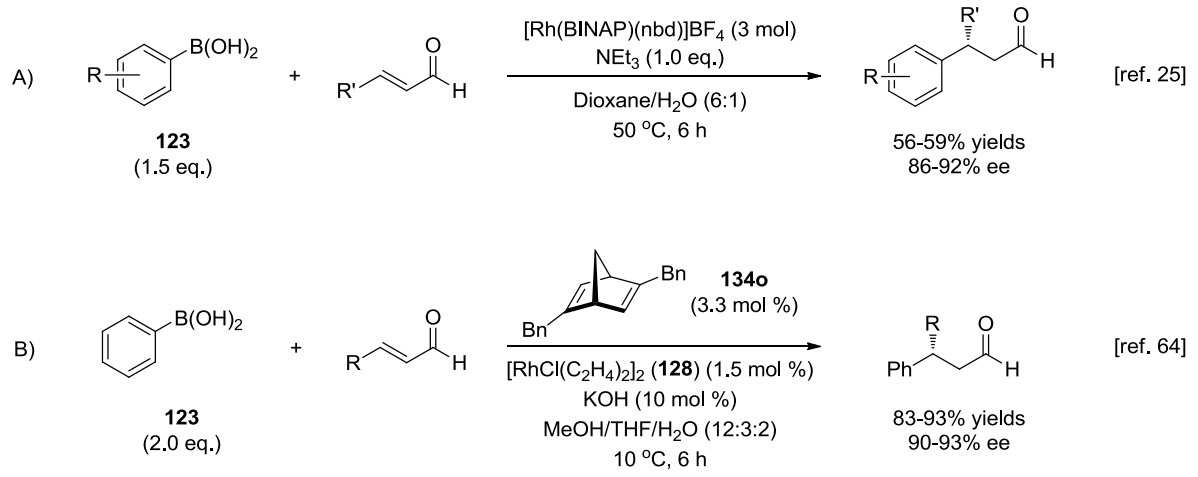
Table 13. Steric effects on the reactivity of enamides in 1,4-conjugate addition.

In contrast to enones, enoates, and enamides, enals suffer from a propensity to undergo 1,2-additions as a side-reaction. Significantly, Miyaura and co-workers showed that this chemoselectivity could be tuned towards the 1,4-conjugate addition product by employing a cationic rhodium complex $[Rh(cod)MeCN)_2]BF_4$ (**141**) in aqueous methanol (***Scheme 70***).[61] Conversely, a single product arising from 1,2-addition could be obtained by employing a neutral rhodium complex $Rh(acac)(coe)_2$ (**142**) in aqueous DME in presence of $^tBu_3P$ (**143**).



Scheme 70. Solvent effects in the chemoselectivity of enals under rhodium catalysis.

High enantioselectivity can be achieved through the use of a chiral BINAP ligand (**129**) but at the expense of yield (***Scheme 71A***).[25] Chiral diene ligands such as **134o** however, have been shown to give improved yields while maintaining the same level of selectivity (***Scheme 71B***).[62]



Scheme 71. Enantioselective 1,4-conjugate addition to enals.

Other acceptors such as nitroalkenes (**144**),[63] alkenyl sulfones (**145**),[64-66] alkenyl phosphonates (**146**),[67] sulfinamides (**147**),[68,69] 4-nitrobenzenesulphonylimines (**148**),[70] *N*-phosphinonyl aldimines (**149**),[71] oxonorbornene derivatives (**150**),[72] and oxabicyclic alkenes (**151**)[73,74] have also been employed in this 1,4-conjugate addition methodology (***Figure 14***).

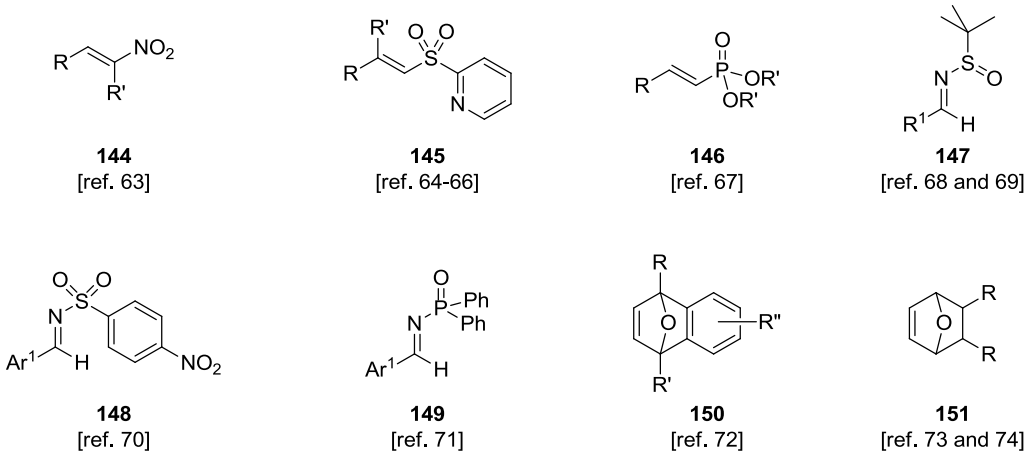
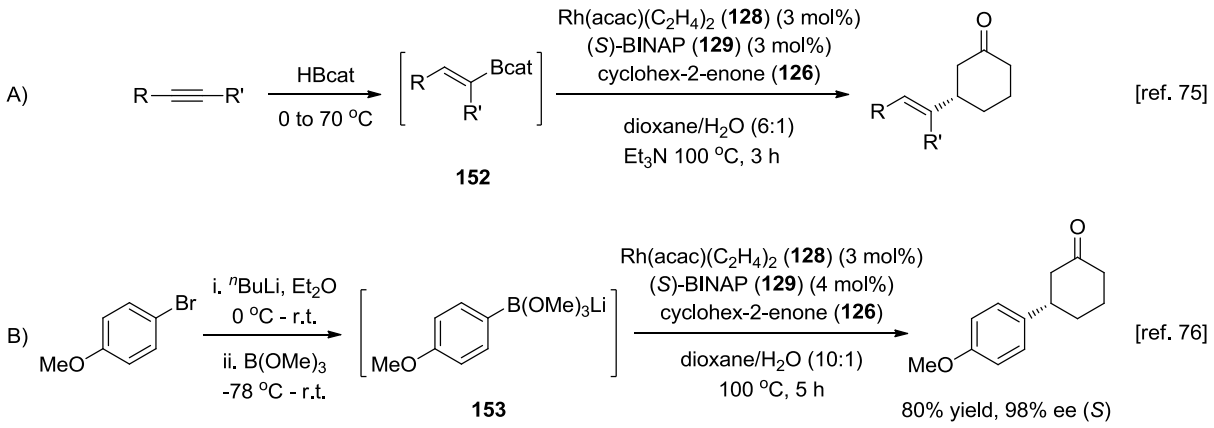


Figure 14. Alternative acceptors in rhodium-catalysed 1,4-conjugate addition reactions.

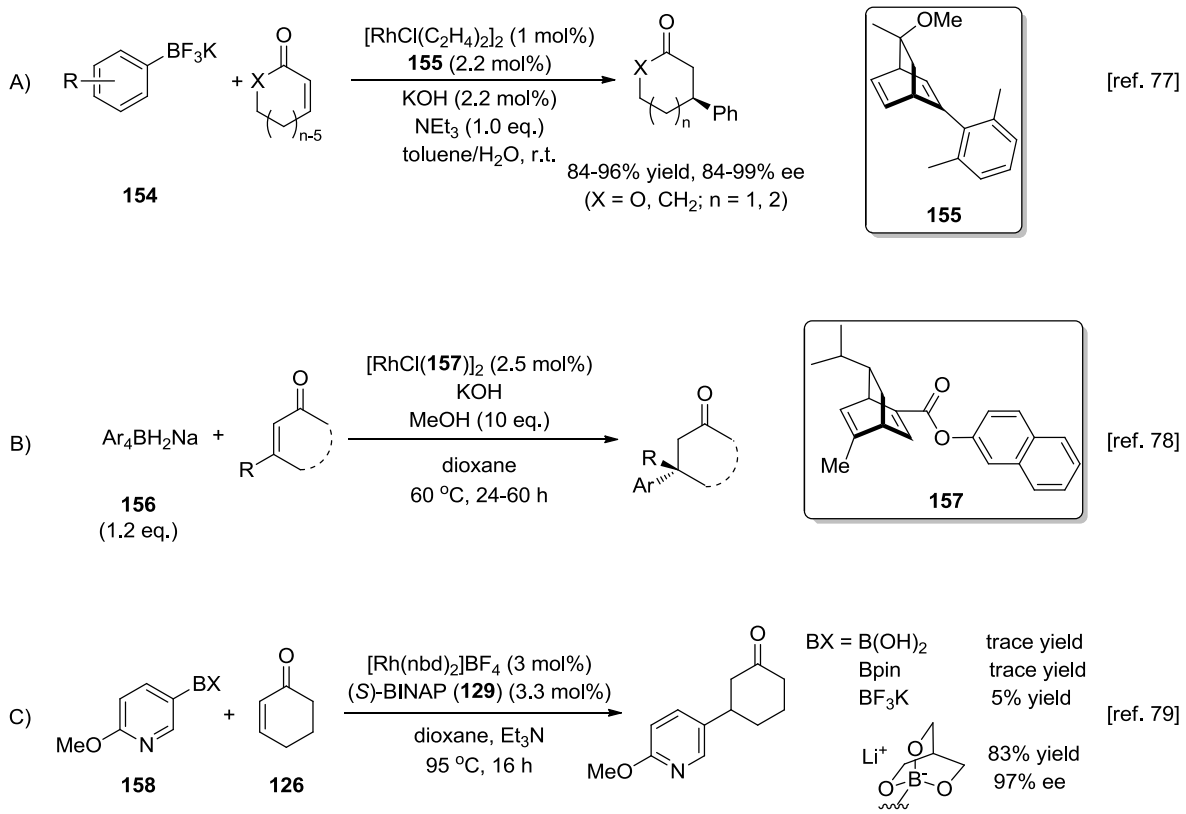
4.2.4 Boryl Donors

Due to the wide range of commercially available boronic acids, boryl donors have become the reagent of choice for many of the rhodium-catalysed 1,4-conjugate addition reactions described thus far. However, as these reactions typically employ aqueous conditions at elevated temperature, high excess of the boronic acid is required to compensate for the competing protodeboronation process. Consequently, boronate ester derivatives such as alkenyl catechol boronate esters (**152**) (***Scheme 72A***)[75] and lithium trimethoxyborates (**153**) (***Scheme 72B***)[76] have been explored as alternative nucleophiles.



Scheme 72. Rhodium-catalysed 1,4-cojugate additions on *in-situ* formed alkenyl catechol boronate esters and aryl lithium trimethoxyboronate species.

Owing to their facile transmetalation to rhodium, potassium organotrifluoroborates (**154**) are also finding wide use in rhodium-catalysed 1,4-conjugate addition reactions (***Scheme 73A***).[77] Similarly, successes have also been found with sodium tetraarylborates (**156**) (***Scheme 73B***).[78] For the notoriously unstable heteroaryl boronate esters, however, only the cyclic triolborates (**158**) developed by Miyaura are sufficiently resistant to protodeboronation (***Scheme 73C***).[79]

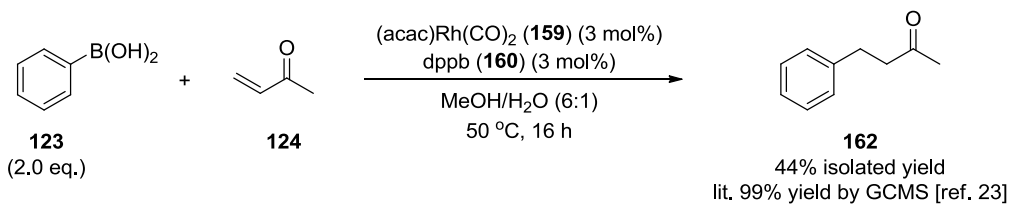


Scheme 73. Alternative boryl donors in Rh-catalysed 1,4-conjugate addition reactions.

4.3 Results and Discussion

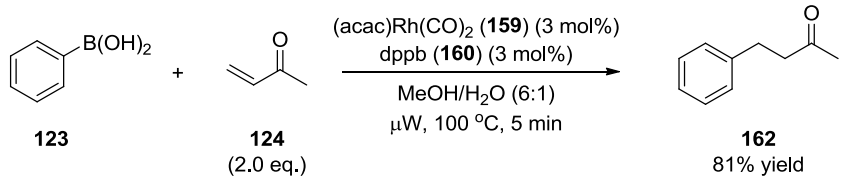
4.3.1 Preliminary Work on the Rhodium-Catalysed 1,4-Conjugate Addition Reaction

In order to explore the 1,4-conjugate addition step as an independent reaction, initial work in this area began with repeating Miyaura's original observation (***Scheme 74***).[23] This involved the addition of water and MVK (**124**) to a stirred methanolic solution of $Rh(acac)(CO)_2$ (**159**) (3 mol%), dppb (**160**) (3 mol%) and phenylboronic acid (**123**) (2.0 eq.) in a Young's tube in a glovebox. The reaction mixture was heated at 50 ˚C in a preheated aluminium heating block for 16 h, cooled to room temperature, extracted into toluene, and concentrated. Following flash column chromatography of the resultant crude mixture, only 44% yield of the desired ketone **162** was obtained in comparison to Miyaura's reported 99% GC-MS yield. The product was easily identified by a peak at *m*/*z* = 148 in GC-MS and two triplets showing complementary coupling constants (^3J = 8.0 Hz) at δ 2.90 and δ 2.76 ppm in the ^{1}H NMR spectrum. This is further supported by a large sharp peak in IR at 1720 cm^{-1}, consistent with a saturated carbonyl stretch.



Scheme 74. Rh-catalysed 1,4-conjugate addition of phenylboronic acid to MVK.

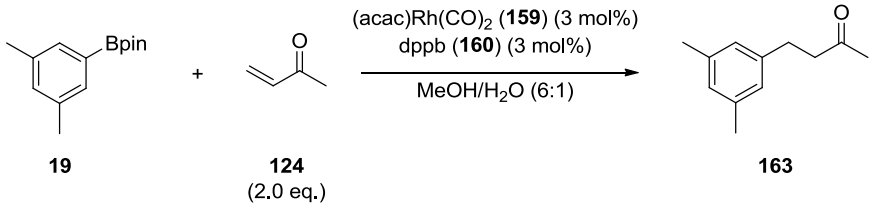
For the purpose of array synthesis it would be more efficient if the arene component was the limiting reagent. Consequently, the procedure was modified to use an excess of acceptor **124**. Simultaneously, in order to accelerate the reaction, the use of a microwave reactor was also explored. This involved conducting the reaction in a crimp top microwave vial rather than a Young's tube. Pleasingly, the use of a 2:1 ratio of phenylboronic acid:MVK in a microwave reactor at 100 ˚C required only 5 minutes for complete consumption of the boronic acid **123** (***Scheme 75***). Significantly protodeboronation did not appear to be problematic, and an excellent 81% isolated yield of ketone **162** was obtained following purification by flash column chromatography.



Scheme 75. Rh-catalysed 1,4-conjugate addition under microwave-irradiation.

Following this result, it was proposed that similar microwave effects should apply to the related pinacol boronate esters which, as products of iridium-catalysed C-H borylation, would be more relevant to the development of array synthesis. To investigate this, the 1,4-conjugate addition reactions of *m*-xylylBpin (**19**) and MVK (**161**) was conducted under both conventional heating using a preheated aluminium block and in a microwave reactor at two different temperatures (***Table 14***). The conjugate addition reaction was regularly monitored by TLC until complete disappearance of the boronate ester **19** was observed. Following purification, similar levels of isolated yields of ketone **163** were obtained across all four

reactions (69-75%). Significantly, consistent with the microwave effects for phenylboronic acid (**123**), substantial acceleration was observed under microwave heating (***Table 14***, entry 1 vs. 2 and 3 vs. 4) particularly at the lower temperature (***Table 14***, entries 3 and 4). It should be noted that microwave acceleration in rhodium-catalysed 1,4-conjugate addition has only been previously reported for boronic acids with acrylates and enamides as acceptors.[51,80,81]



entry	temp (˚C)	heating method	time (min)	isolated yield (%)
1	100	conventional	16	69
2	100	μW	6	75
3	60	conventional	120	73
4	60	μW	20	72

Table 14. Temperature and microwave effects on Rh-catalysed 1,4-conjugate addition.

To develop a more convenient analytical method in future work, *m*-xylylBpin (**19**) was calibrated against ^{n}hexadecane (**164**) as an internal standard in GC-MS analysis (***Figure 15***). Such calibration is required to account for the variation in response factors of these compounds under FID. ^{n}Hexadecane (**164**) was chosen as an internal standard as it is chemically inert, has a molecular mass large enough to be easily detected, gives a sharp signal on the TIC trace and, most importantly, has retention time which is well away from any other components of the conjugate addition reaction. By plotting different molar ratios of **19** and **164** against the corresponding area ratio on the TIC trace, a mathematical

relationship could be obtained, which allows for the quantification of *m*-xylylBpin in the presence of a known amount of the internal standard.

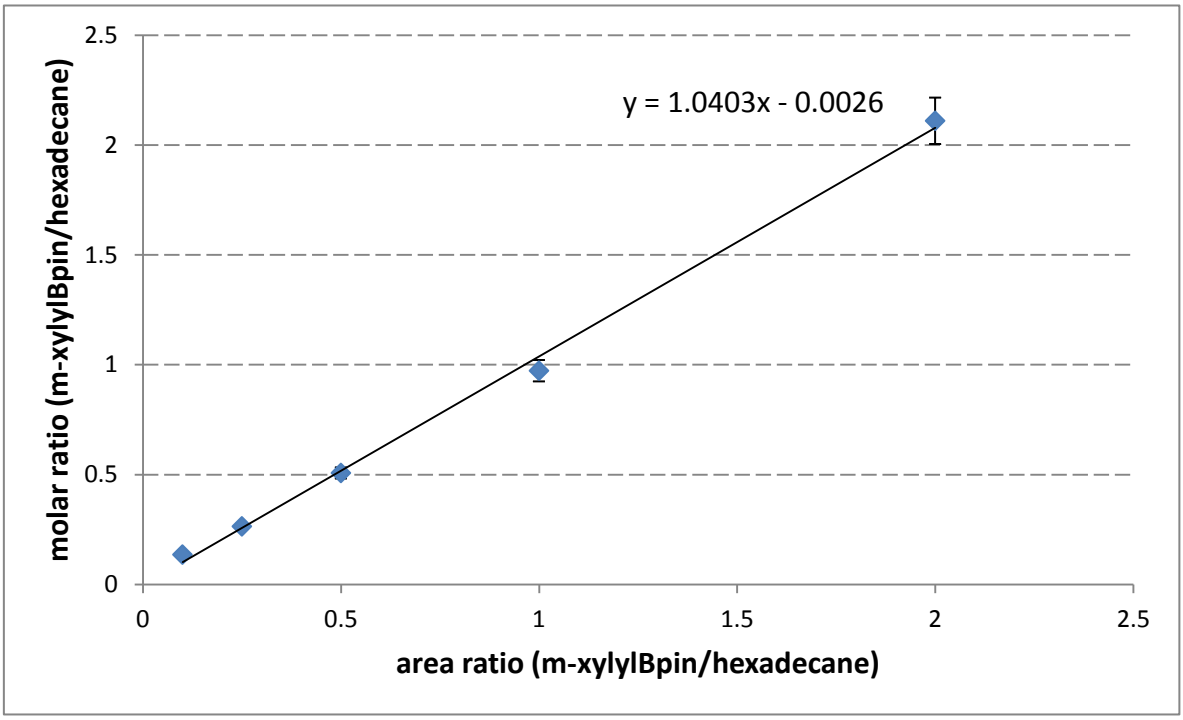
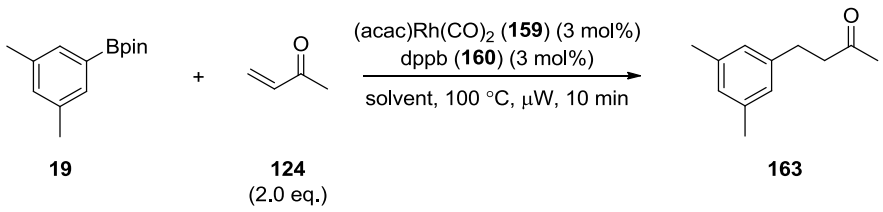


Figure 15. GC-MS calibration of *m*-xylylBpin with ^{n}hexadecane as an internal standard.

With this analytical method in hand, optimisation of the rhodium-catalysed 1,4-conjugate addition on the boronate ester **19** and MVK (**124**) was explored using a range of solvent systems. Among these THF and MTBE solvents were chosen as they are commonly used in iridium-catalysed C-H borylation and could therefore provide early indications on whether they could be used as a single solvent for both the borylation and the 1,4-conjugate addition reactions. However, reduction of the water content (***Table 15***, entry 1) or replacement of methanol with either THF (***Table 15***, entry 2) or MTBE (***Table 15***, entry 3) at 100 ˚C under microwave heating led to poor conversions of **19** (21-26% by GC-MS). Following these results, both methanol and water components of the original solvent mixture appear to be

important. Consistent with this, the 1,4-conjugate addition reaction was completely inhibited in MTBE solvent in the absence of both methanol and water (***Table 15***, entry 4).



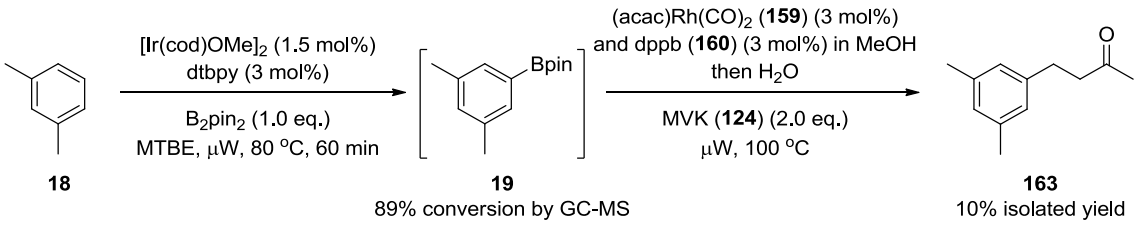
entry	solvent	GC-MS conv. (%)
1	wet MeOH	21
2	THF/H_2O (6:1)	26
3	MTBE/H_2O (6:1)	23
4	MTBE	0

Table 15. Solvent effects in the rhodium-catalysed 1,4-conjugate addition.

4.3.2 Rh(acac)$(CO)_2$ in Iridium-Catalysed Aromatic C-H Borylation/Rhodium-Catalysed 1,4-Conjugate Addition Sequence

Having established that both methanol and water are important to the rhodium-catalysed 1,4-conjugate addition, initial attempts to achieve a sequential borylation/conjugate addition process simply involved subjecting the reaction mixture obtained from the borylation of *m*-xylene (**18**) to the conjugate addition conditions (***Scheme 76***). To maximise the efficiency of this sequence, Harrisson's previously reported microwave-accelerated protocol was used for the borylation step. This involved charging a crimp top microwave vial with m-xylene (**18**) (1.0 mmol) followed by the addition of an aliquot of preformed stock solution of the catalyst containing $[Ir(cod)OMe]_2$ (1.5mol%), dtbpy (3 mol%), MTBE (2.4 mL)

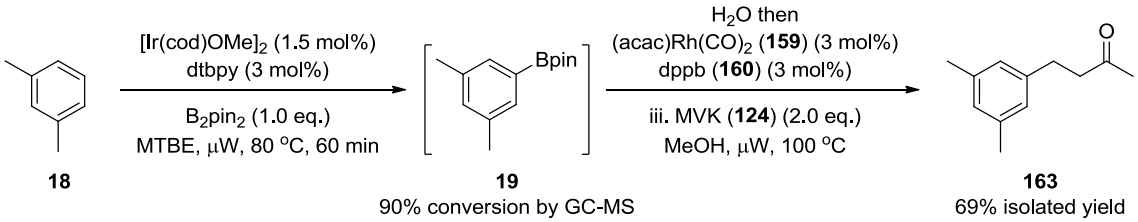
and B_2pin_2 (1.0 eq.) in a glovebox. The tube was then heated in a focused microwave reactor at 80 ˚C for 1 h, leading to 89% conversion (GC-MS) to *m*-xylylBpin (**19**). To initiate the conjugate addition reaction, a methanolic solution of **159**/**160** (3 mol%), water and MVK (**124**) were added, in sequence, directly to this reaction mixture. However, following microwave heating at 100 ˚C for 20 minutes, aqueous workup and flash column chromatography, only a 10% isolated yield of the desired ketone **163** was obtained.



Scheme 76. Initial attempt to facilitate C-H borylation/1,4-conjugate addition sequence.

In an effort to determine the cause of this low yield, the GC-MS trace at the crude stage was reanalysed and a significant level of *m*-xylene (**18**) arising from protodeboronation of *m*-xylylBpin (**19**) was observed. This suggested that although protodeboronation is negligible in the rhodium-catalysed conjugate addition step as a standalone reaction, it becomes problematic in presence of additional components from the borylation step. With this in mind, a method to quench the borylation mixture prior to initiating the 1,4-conjugate addition was considered. It was noted that effervescence was observed following addition of the methanolic solution in the original sequence, probably as a result of partial quenching of the borylation mixture. It was postulated that this may have a deleterious effect on the rhodium catalyst. By simply switching the sequence of addition so that water is used to facilitate the initial quenching, and that the addition of the methanolic solution of **159** and

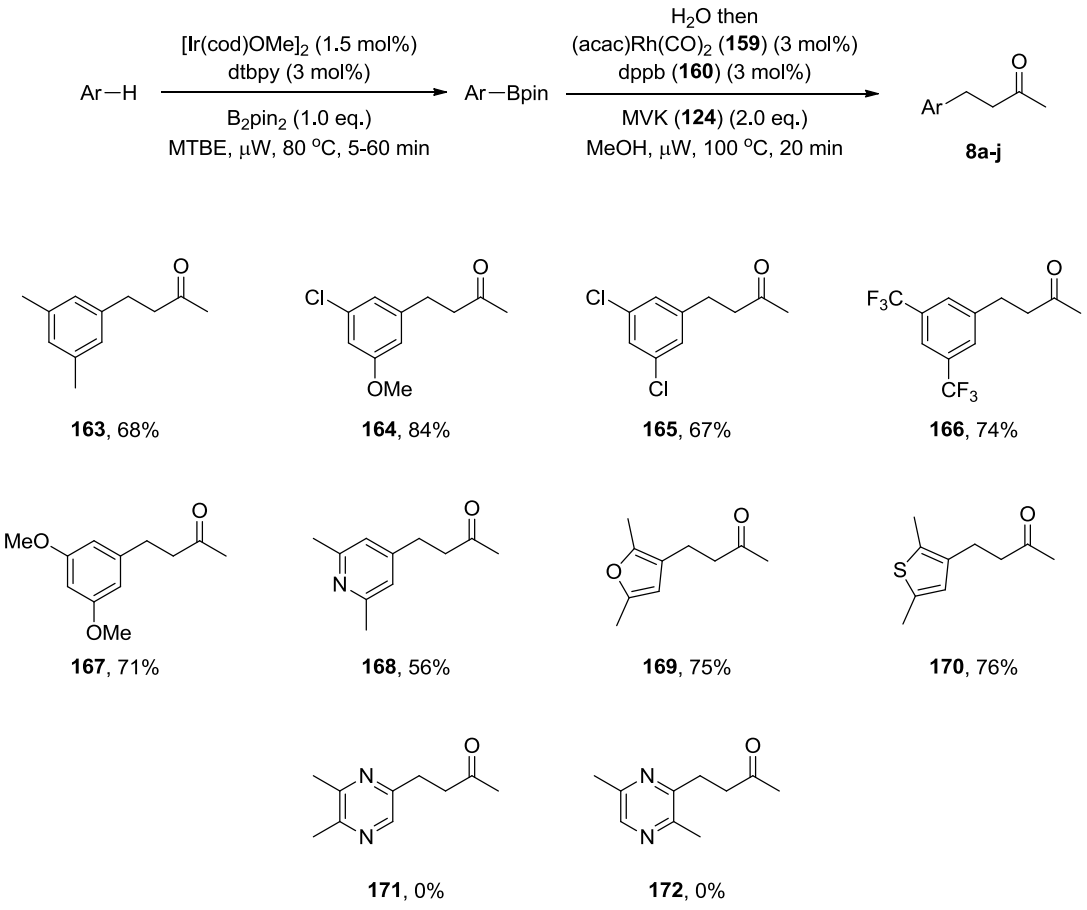
160 was only carried out once the resultant effervescence has completely stopped, it was hoped that the reactivity of the 1,4-conjugate addition could be recovered. Satisfyingly, under these modified conditions, a much improved 69% isolated yield of the desired ketone **163** was obtained (***Scheme 77***). Considering that the initial borylation reaction underwent 90% conversion (by GC-MS), this final yield represented an excellent 77% conversion in the second step. The quenching action of the water on the borylation mixture is not known, however, its importance has also been previously reported in Harrisson's thesis on the development of borylation/Suzuki-Miyaura cross-coupling sequence.[82]



Scheme 77. Quenching of the borylation step with water prior to initiating the second step.

Having established an efficient protocol for the C-H borylation/1,4-conjugate addition sequence on *m*-xylene (**18**) and MVK (**124**), a range of suitable borylation substrates was explored (***Scheme 78***). For simplicity, arenes that are known to give a single borylation product, such as 1,3-disubstituted benzenes and 2,5-disubstituted 5-ring membered heteroaromatics were used, with MVK (**124**) as acceptor. Satisfyingly, excellent isolated yields of the desired ketones **163-172** (up to 84%), were obtained from the reactions of both electron-rich and electron-poor 1,3-disubstituted benzenes as well as heteroarenes. Although pyrazines underwent the initial borylation reaction efficiently, the resultant α-

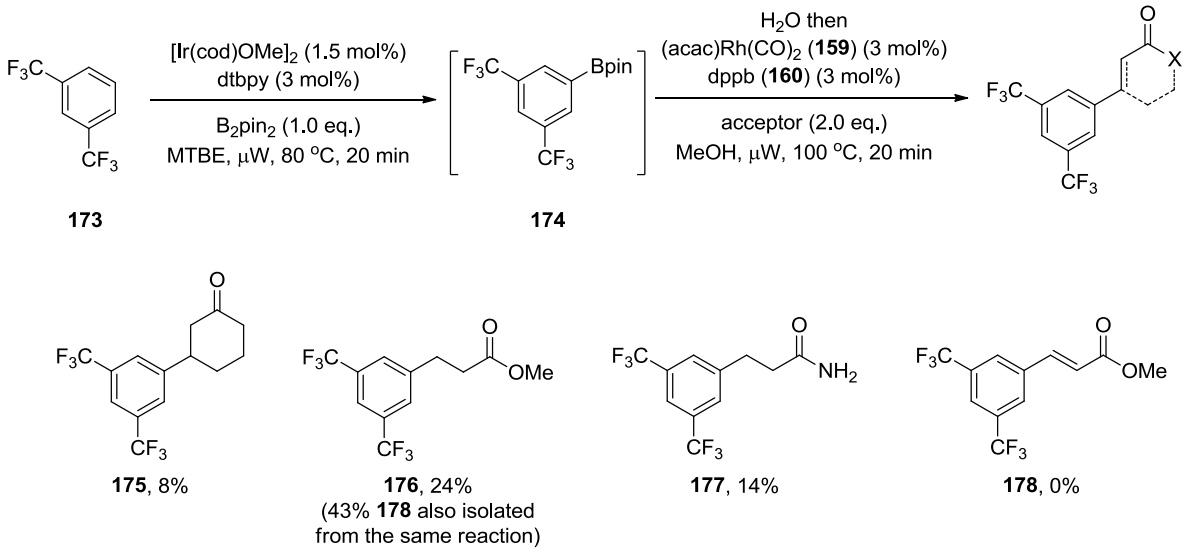
pyridyl boronate esters were unstable to the conditions of the subsequent 1,4-conjugate addition step, and so ketones **171** and **172** were not found.



Scheme 78. Screening of arenes in the C-H borylation/1,4-conjugate addition sequence.

Following these promising results, a range of alternative acceptors was explored including a cyclic β-substituted enone, enoate, enamide, and alkynoate (***Scheme 79***). To simplify analysis and product characterization, fluorine-containing 1,3-bis(trifluromethyl)benzene (**173**) was used as the arene substrate. Disappointingly, poor conversion was observed in the second step across all of the acceptors tested. In particular, the use of methyl propiolate did not lead to any discernable formation of product **178**. Although the poor reactivity of cyclohex-

2-enone (**126**) has been previously reported in Miyaura's original work on $Rh(acac)(CO)_2$ (**159**), the low conversion involving methyl acrylate (**179**) was unprecedented given that enoates appeared to be almost as reactive as enones in the same report.[23]



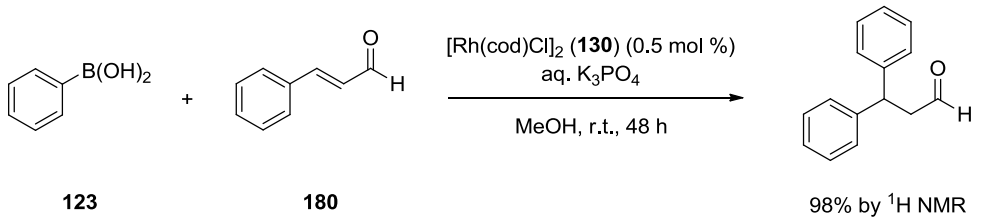
Scheme 79. Screening of acceptors in the C-H borylation/1,4-conjugate addition sequence.

Interestingly, in the reaction involving the enoate **179**, a significant amount of a side-product **178** was isolated in 43% yield. This was identified by two doublets with complementary coupling constants (^3J = 15 Hz) at δ 6.61 ppm and δ 7.43 ppm in the ^{1}H NMR. These chemical shifts and coupling constants are consistent with trans olefinic protons. A peak on the GC-MS with *m*/*z* = 162 also supports the proposed structure. While this oxidative Heck transformation has considerable precedence using palladium chemistry, it is not so well documented with rhodium catalysts.[83] This and the lack of such product in Miyaura's original 1,4-conjugate addition protocol,[23] suggest that the oxidative 'Heck' side-product **178**, was

not promoted *via* a rhodium complex, but possibly through a combination of both rhodium and iridium complexes.

4.3.3 Evaluation of $[Ir(cod)OMe]_2$ and $[Rh(cod)Cl]_2$ as a Single Catalyst Precursor for the Borylation/1,4-Conjugate Addition Sequence

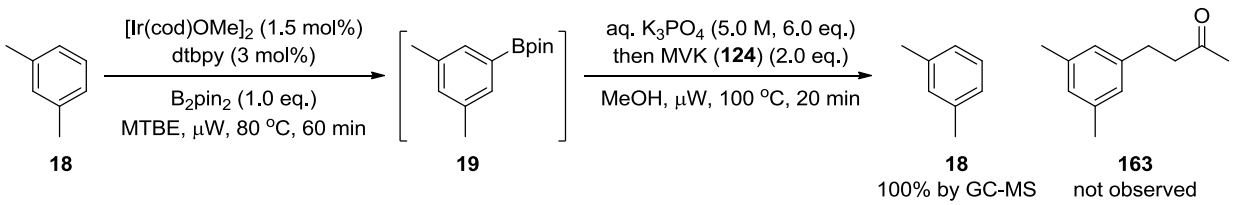
The low reactivity of the 1,4-conjugate addition step above towards acceptors other than MVK (**161**), prompted the search for a more reactive and efficient catalyst systems. One catalyst precursor which stood out in the literature was $[Rh(cod)Cl]_2$ (**130**), as it displays high efficiency and significantly, can function in array chemistry in the absence of added ligand. For example, Hu and co-workers showed that 1 mol% of this complex catalysed the 1,4-conjugate addition of phenylboronic acid (**123**), and cinnamaldehyde (**180**) in excellent 98% yield (***Scheme 80***).[84]



Scheme 80. Rhodium-catalysed 1,4-conjugate addition using $[Rh(cod)Cl]_2$.

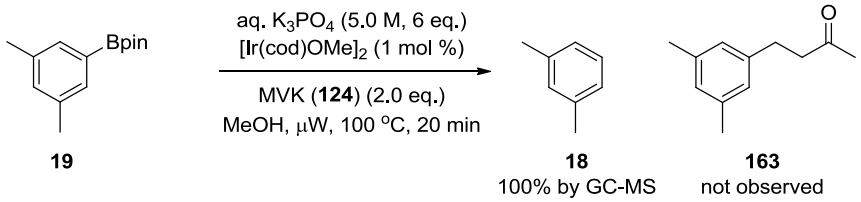
Given the similar electronic configuration of this complex and $[Ir(cod)X]_2$ (both rhodium and iridium occupy the same group in the periodic table), it was speculated that $[Ir(cod)OMe]_2$, could potentially be used as a single catalyst precursor for both steps of the borylation/1,4-

conjugate addition sequence. To test this theory, the previously developed sequence was modified to exclude the $Rh(acac)(CO)_2$ precursor (**159**) and dppb ligand (**160**), with H_2O replaced by 5.0 M aq. K_3PO_4. Although the addition of base is known to have detrimental effects on the catalyst generated from $Rh(acac)(CO)_2$, there is considerable precedence for accelerated reaction rates when used in combination with $[Rh(cod)Cl]_2$ (**130**) as a catalyst precursor. Disappointingly, however, complete protodeboronation of *m*-xylylBpin (**19**), was observed (GC-MS) following the second step (***Scheme 81***).



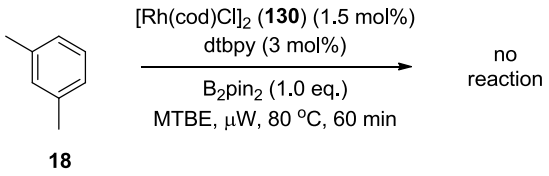
Scheme 81. C-H borylation/1,4-conjugate addition sequence in the absence of rhodium complexes.

This result suggested that iridium complexes do not promote 1,4-conjugate addition of arylboronates esters. Consistent with this, complete protodeboronation was also observed when the second step was carried out as an independent reaction on a purified sample of the boronate ester **19** (***Scheme 82***).



Scheme 82. An attempt to catalyse 1,4-conjugate addition using [Ir(cod)OMe]$_2$.

Following these results, the related [Rh(cod)Cl]$_2$ (**130**) was explored as a catalyst precursor for the borylation of *m*-xylene (**18**) (***Scheme 83***). This simply involved replacing [Ir(cod)OMe]$_2$ directly with [Rh(cod)Cl]$_2$ (**130**) in the typical borylation protocol. However, no reaction was observed indicating that the sequence required the two discrete catalytic species.

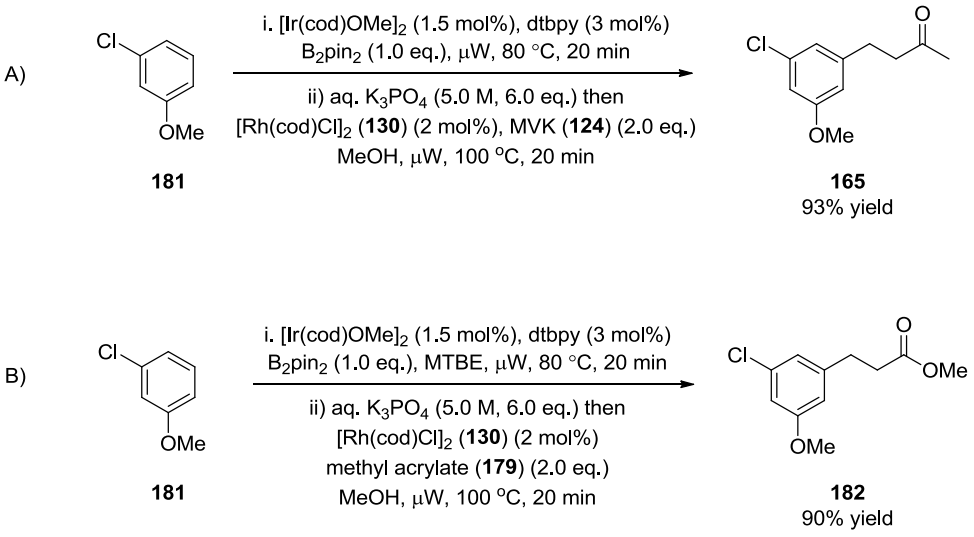


Scheme 83. An attempt to borylate *m*-xylene using [Rh(cod)Cl]$_2$.

4.3.4 Preliminary Work on C-H Borylation/1,4-Conjugate Addition Sequence with [Rh(cod)Cl]$_2$

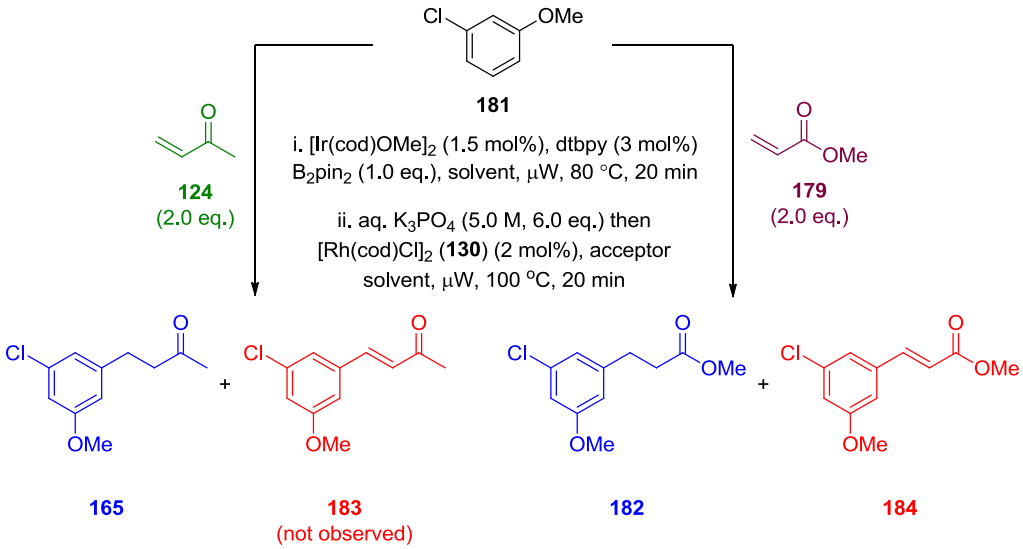
Having established that it was not possible to use either [Ir(cod)OMe]$_2$ or [Rh(cod)Cl]$_2$ (**130**), as a single catalyst precursor for both the borylation and 1,4-conjugate addition reactions, attention returned to the original strategy of using both precursors in the sequence. Initial work on this simply involved replacing Miyaura's original 1,4-conjugate addition conditions with those reported by Hu and co-workers in the one-pot sequence described in section

4.3.2 (***Table 3***). In these reactions employing 3-chloroanisole (**181**) as the starting material, the quenching of the borylation mixture was facilitated using aq. K_3PO_4 prior to the 1,4-conjugate addition step. Under these conditions, and with MVK (**124**), as acceptor, an excellent 93% isolated yield of the desired ketone **165** was obtained (***Scheme 84A***). This represents a marked improvement on the 84% yield obtained with Rh(acac)$(CO)_2$ (**159**) as the catalyst precursor (***Scheme 78***). Significantly, excellent 90% yield was also obtained with methyl acrylate (**179**) as acceptor (***Scheme 84B***). This is again a remarkable achievement given that the same reaction with methyl acrylate in the previous one-pot sequence (albeit with **173** as the arene starting material) afforded the ester product **182** in only 24% yield. Moreover, the lack of oxidative Heck product in this reaction only serves to demonstrate the greater reactivity of the catalyst derived from $[Rh(cod)Cl]_2$ (**130**) when compared to Rh(acac)$(CO)_2$ (**159**).



Scheme 84. Initial attempts to conduct one-pot C-H borylation/1,4-conjugate addition sequence using $[Rh(cod)Cl]_2$ in the second step.

Since for the purpose of one-pot reactions it would be more efficient to use a single solvent, attempts were subsequently made to replace methanol in the second step. Although previous attempts to do this on the sequence employing catalyst precursor **159** was unsuccessful, THF has been reported as a suitable solvent for $[Rh(cod)Cl]_2$ (**130**). With this in mind, both borylation-compatible THF and MTBE were used as single solvents in the one-pot sequence with MVK (**124**), and methyl acrylate (**179**), employed as acceptors (***Table 16***). While excellent yields of ketones **165** and **183** were retained for the reactions with MVK (**124**) (***Table 16***, entries 1 and 3), a significant drop in yield were obtained with methyl acrylate (**179**) owing to the formation of oxidative Heck products **183** and **184** (***Table 16***, entries 2 and 4). Following these results, further attempts to optimize the one-pot sequence by reducing the amounts of acceptor or base, were made on the more promising two-solvent system. Pleasingly excellent isolated yield was maintained when the amount of acceptor **124** was reduced from two to one equivalent (***Table 16***, entry 5). However, a combination of this and the reduction of K_3PO_4 base from six to three equivalents led to lower 80% yield due to increased amounts of protodeboronation (***Table 16***, entry 6).



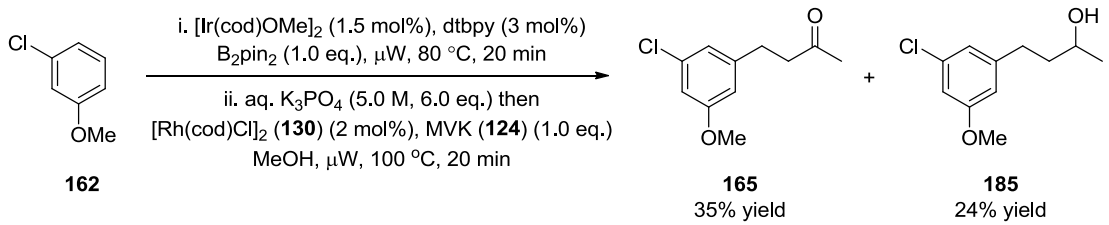
	solvent				isolated yields[a]	
entry	step i.	step ii.	K_3PO_4	acceptor (eq.)	CA (%)	OH (%)
1	MTBE	MTBE	6.0 eq.	**124** (2.0)	**165** (96)	**183** (0)
2	MTBE	MTBE	6.0 eq.	**179** (2.0)	**182** (82)	**184** (10)
3	THF	THF	6.0 eq.	**124** (2.0)	**165** (96)	**183** (0)
4	THF	THF	6.0 eq.	**179** (2.0)	**182** (71)	**184** (26)
5	MTBE	MeOH	6.0 eq.	**124** (1.0)	**165** (92)	**183** (0)
6	MTBE	MeOH	3.0 eq.	**179** (1.0)	**182** (80)	**184** (0)

[a]CA = 1,4-conjugate addition product, OH = Oxidative 'Heck' product.

Table 16. Solvent effects in one-pot C-H borylation/1,4-conjugate addition sequence.

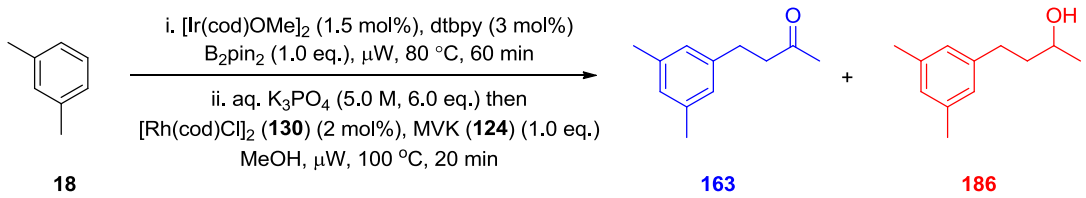
However, subsequent attempts to repeat this sequence led to substantially lower yield (*ca.* 35%) of the desired ketone **165** (***Scheme 85***). In these reactions, a substantial amount of the corresponding alcohol product **185**, was also isolated, clearly as a result of an unprecedented reduction of the initially formed ketone. This alcohol product could be clearly ascertained by GC-MS (*m*/*z* = 176) and the chiral carbinol proton signal at δ 3.84 ppm on ^{1}H NMR spectrum. While the difference between these latter set of results and in earlier work is not clear, it was quickly recognised that if the reduction process could be suppressed

or encouraged, selective formation of either the ketone or the alcohol products could be achieved.



Scheme 85. Unprecedented alcohol side-product generated in the one-pot C-H borylation/1,4-conjugate addition sequence.

For the reduction process to occur, a source of hydride is required. On this basis, it was speculated that H_2 or HBpin, generated from the arene borylation, could be involved in this reductive pathway. Using *m*-xylene (**18**) as the borylation substrate, an initial attempt to improve the ketone yield through expulsion of H_2 by applying a continuous flow of nitrogen in the head space of the reaction vessel prior to addition of the enone **124** was unsuccessful (***Table 17***, entry 1). Prolonging of the quenching time to ensure complete decomposition of residual HBpin also failed to inhibit the formation of the alcohol product **185** (***Table 17***, entry 2). Interestingly, the combination of these modifications led to an increased methanol concentration, owing to evaporation of some of the MTBE, resulting in a higher proportion of **186** (***Table 17***, entry 3). This suggested that the reduction proceeds *via* transfer hydrogenation with the MeOH serving as the hydrogen source.



18 163 186

		isolated yield (%)	
entry	modifications	**163**	**186**
1	expel H_2	40	24
2	extended quenching time	37	30
3	expel H_2 + extended quenching time	14	51

Table 17. Initial attempts to suppress the formation of alcohol side-product.

4.3.5 Mechanistic Studies

In order to confirm this hypothesis, deuterated methanol, CD_3OH and CD_3OD, were used in the second step of the sequence. The ketone and alcohol products were analysed for deuterium incorporations by comparing the signal strengths of the residual proton of the deuterated carbon against the aromatic signals in the ^1H NMR spectrum (***Figure 16***).

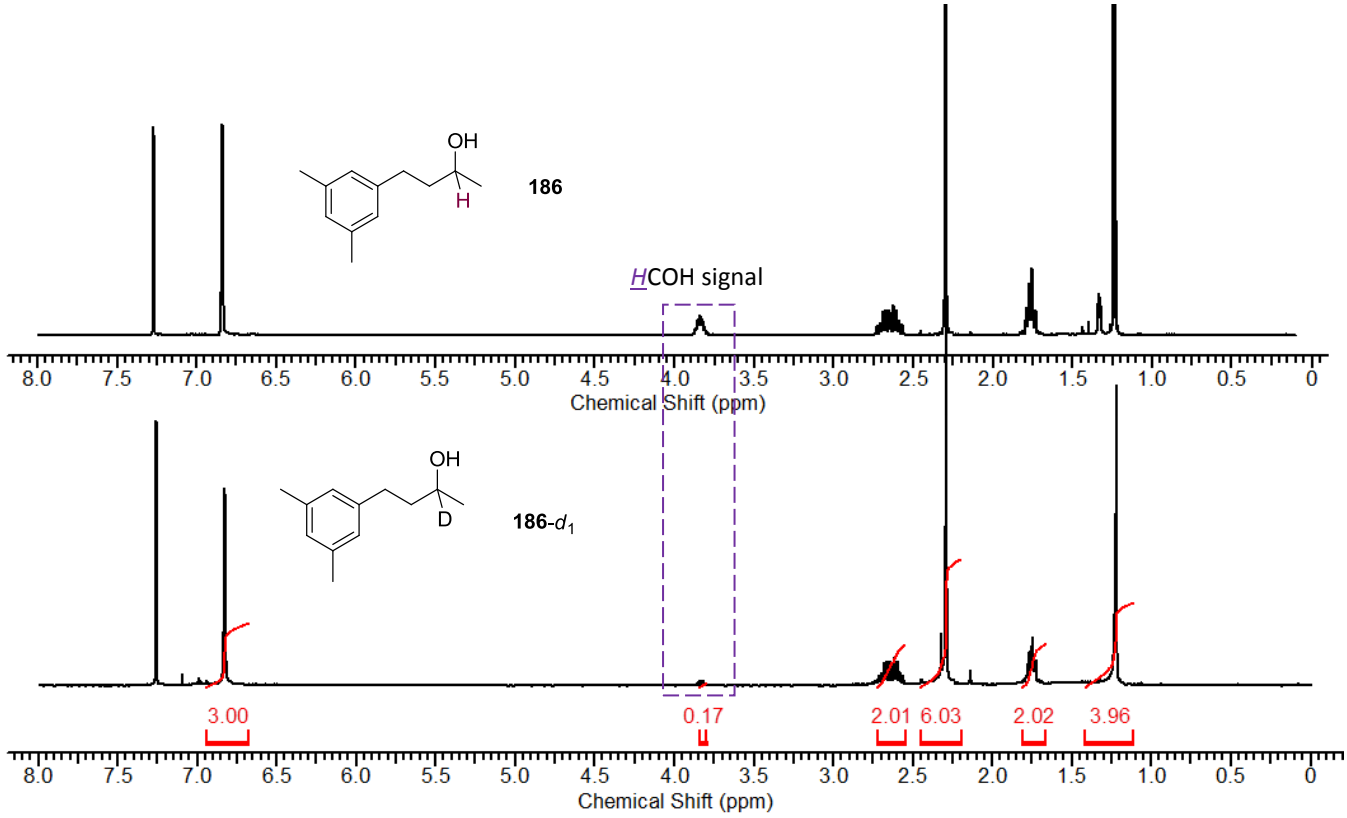
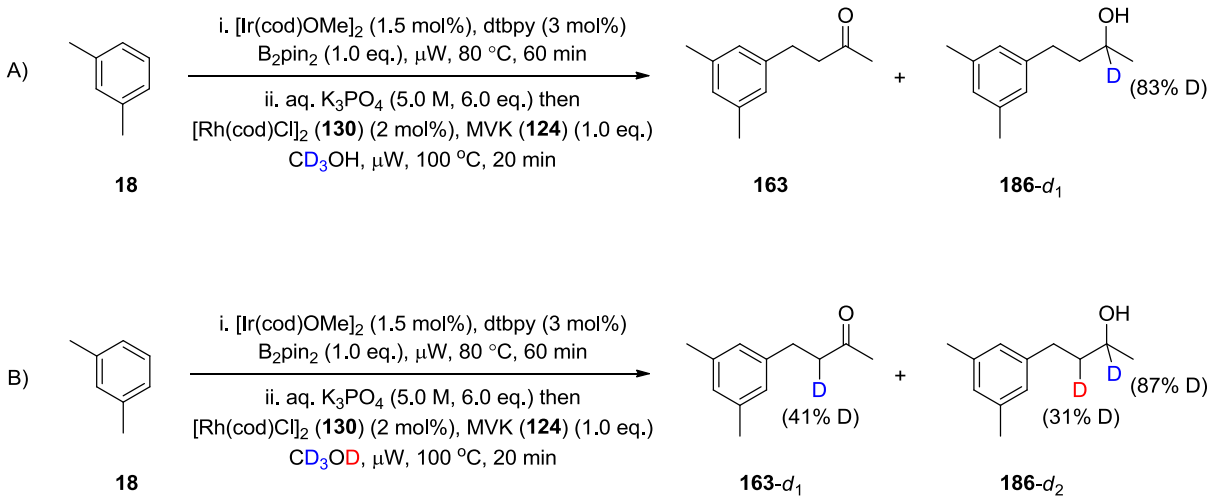


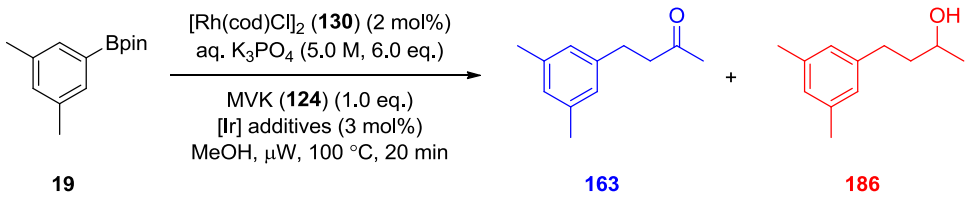
Figure 16. Evidence for deuterium incorporation.

From these reactions, high deuterium incorporation (>80%) was observed at the carbinol carbon of the alcohol product **186** (***Scheme 86***). These results are consistent with the proposed reductive pathway with MeOH as the hydrogen source in transfer hydrogenation. Low level of deuterium incorporation at the adjacent carbon of the ketone and alcohol products from the sequence employing CD_3OD was attributed to the participation of the labile deutero in the hydrolysis step of the 1,4-conjugate addition. Conversely there was a complete lack of deuterium incorporation at this position when CD_3OH was used.



Scheme 86. Percent deuterium incorporation.

Further studies showed that the transfer hydrogenation process requires an iridium complex to be present (***Table 18***). Reduction was suppressed by filtering the reaction mixture through silica gel prior to the 1,4-conjugate addition step (***Table 18***, entry 1). While addition of $[Ir(cod)OMe]_2$ (***Table 18***, entry 2) or a combination of this with dtbpy (***Table 18***, entry 3) in the rhodium-catalysed conjugate addition of *m*-xylylBpin (**18**), to MVK (**124**), resulted in no alcohol product (**186**) being detected, the addition of a premixed solution of B_2pin_2, $[Ir(cod)OMe]_2$ and dtbpy led to the alcohol product being observed once again (***Table 18***, entry 4).

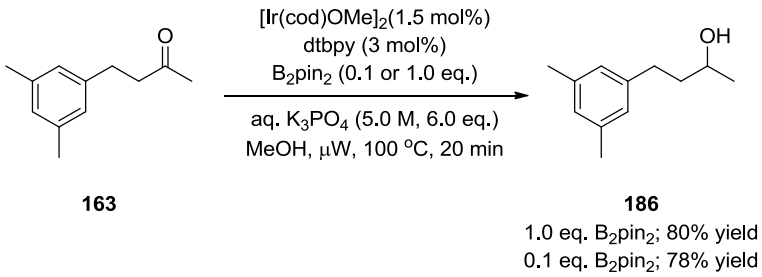


		isolated yield (%)	
entry	[Ir]	**163**	**186**
1	none[a]	56	0
2	$[Ir(cod)OMe]_2$	63	0
3	½$[Ir(cod)OMe]_2$/dtbpy	66	0
4	½$[Ir(cod)OMe]_2$/dtbpy (3 mol%)+ B_2pin_2 (1.0 eq.)	45	10

[a]1,4-Conjugate addition was carried out following rapid filtration of the borylation reaction mixture through a short plug of silica to remove any Ir complexes.

Table 18. Rhodium-catalysed 1,4-conjugate addition of *m*-xylylBpin to MVK in the presence or absence of Ir complexes.

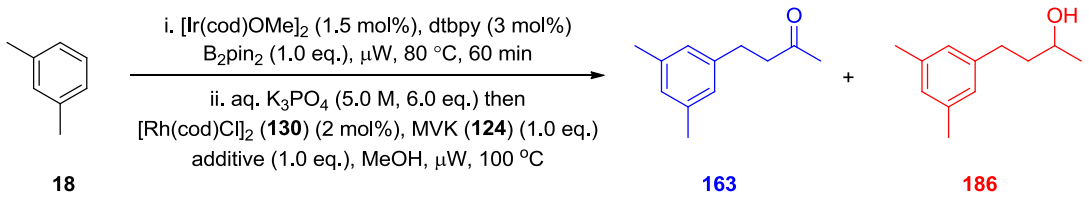
This suggested that the active species responsible for the transfer hydrogenation process is generated through the quenching of the trisboryl iridium complex $[Ir(dtbpy)(Bpin)_3]$ formed in the borylation step. In support of this, reaction of purified *m*-xylylBpin (**19**) with methanol in the presence of the iridium species generated by quenching a mixture of $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and 0.1 or 1 equivalent of B_2pin_2 with aq. K_3PO_4 afforded alcohol **186** in 78 and 80% yields respectively (***Scheme 87***).



Scheme 87. Transfer hydrogenation reduction of ketone using trisboryl iridium complex pre-quenched with aq. K_3PO_4.

4.3.6 Optimisation of the C-H Borylation/1,4-Conjugate Addition Sequence with $[Rh(cod)Cl]_2$

Having identified methanol as the reductant, attempts to optimise the sequence to obtain either the ketone or alcohol product through solvent selection was carried out (***Table 19***). By replacing the methanol solvent in the second step with a solvent such as acetone, MTBE or THF (***Table 19***, entries 1-3), selective formation of the ketone product **163** was achieved. While extended reaction time in MeOH leads to a higher proportion of the alcohol product **188** (***Table 19***, entry 4), superior reaction rate can be achieved using isopropanol (IPA) as a more efficient hydrogen source (***Table 19***, entries 5 and 6). Introduction of other hydrogen sources, however, were less effective. For example, the addition of 9,10-dihydroanthracene (**187**) did not affect the reaction (***Table 19***, entry 7), while 1,4-cyclohexadiene (**188**) suffers from poor conversion of the boronate ester **19** (***Table 19***, entry 8). Although the alcohol product **186** was obtained exclusively with the addition of ammonium formate (**189**) as hydrogen source, again, poor conversion of the boronate ester **19** was observed (***Table 19***, entry 9).

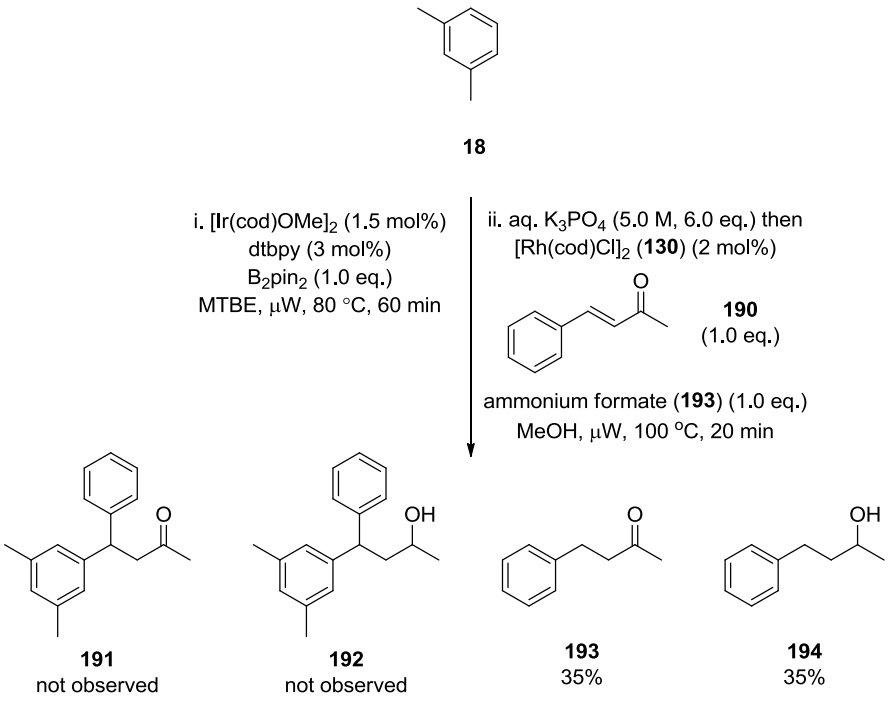


					isolated yield (%)	
entry	base (eq.)	additive[a]	time (min)	solvent	**163**	**186**
1	K_3PO_4 (6.0)	-	20	acetone	73	0
2	K_3PO_4 (6.0)	-	20	MTBE	71	0
3	K_3PO_4 (6.0)	-	20	THF	67	0
4	K_3PO_4 (6.0)	-	150	MeOH	10	42
5	K_3PO_4 (6.0)	-	20	IPA	26	49
6	K_3PO_4 (6.0)	-	60	IPA	6	65
7	K_3PO_4 (6.0)	**187**	20	MeOH	47	17
8	K_3PO_4 (6.0)	**188**	20	MeOH	7	11
9	K_3PO_4 (6.0)	**189**	20	MeOH	0	10

[a] **187** = 9,10-dihydroanthracene, **188** = 1,4-cyclohexadiene, **189** = ammonium formate.

Table 19. Solvent effects in the second step of the C-H borylation/1,4-conjugate addition sequence.

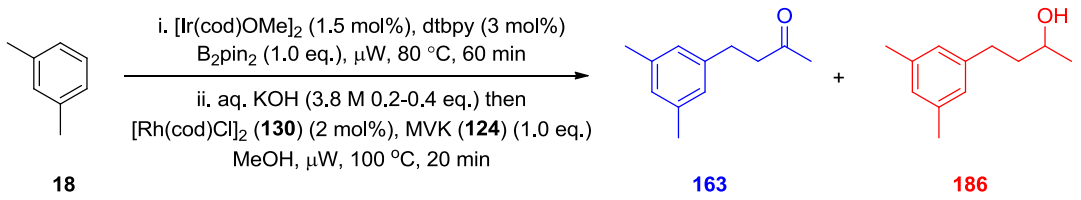
This poor conversion was attributed to the reduction of MVK (**124**), arising from the powerful reducing nature of ammonium formate (**189**). As a confirmation of this, substantial amount of the ketone (**193**) and alcohol (**194**) were isolated from the sequence employing the corresponding methyl styryl ketone (**190**) as acceptor (***Scheme 88***).



Scheme 88. Reduction of the methyl styryl ketone acceptor in the presence of a powerful reducing agent, ammonium formate.

Having resolved the chemoselectivity issues of the sequence through solvent selection, the practical aspect, particularly with regard to array synthesis, was considered. With K_3PO_4 as the base, the highly viscous 5.0 M aq. solution required posed handling difficulties during both the reaction set-up and aqueous work-up. Screening of a stronger Brønsted base, KOH, in the one-pot tandem borylation/1,4-conjugate addition reaction (***Table 20***) showed that indeed only 2.0 eq. is required for optimum performance under non-reducing conditions (***Table 20***, entries 1-6). Slightly lower yield of the alcohol product **188** was obtained under reduced conditions with 2.0 eq. of the KOH base (***Table 20***, entry 7). However, by increasing the reaction time to 80 minutes, complete reduction of the ketone **163** was achieved leading to an improved yield (***Table 20***, entry 7). Significantly, increasing the amount of enone **124** to

2.0 eq. did not lead to superior yields under both reducing and non-reducing conditions (***Table 20***, entries 9 and 10).

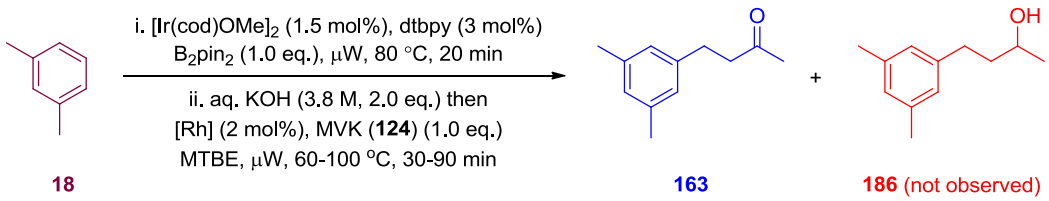


entry	solvent	KOH eq.	MVK **124** eq.	time (min)	isolated yield (%)
1	MTBE	-	1.0	20	**163** (11)
2	MTBE	0.2	1.0	20	**163** (23)
3	MTBE	0.5	1.0	20	**163** (48)
4	MTBE	1.0	1.0	20	**163** (66)
5	MTBE	2.0	1.0	20	**163** (68)
6	MTBE	4.0	1.0	20	**163** (65)
7	IPA	2.0	1.0	20	**186** (52)
8	IPA	2.0	1.0	80	**186** (61)
9	MTBE	2.0	2.0	20	**163** (65)
10	IPA	2.0	2.0	20	**186** (63)

Table 20 KOH as base in the C-H borylation/1,4-conjugate addition sequence.

Further optimisation was sought by comparing the reactivity of the catalyst derived from $[Rh(cod)Cl]_2$ (**130**), against a range of some of the most commonly used rhodium catalyst precursors in 1,4-conjugate addition (***Table 21***). For convenience, these reactions were analysed by LC-MS at the crude stage. While $[Rh(cod)OH]_2$ (**131**), displayed similar level of reactivity to $[Rh(cod)Cl]_2$ (**130**), poorer conversion of *m*-xylyBpin (**19**), was observed for $[Rh(nbd)Cl]_2$ (**193**), and $[Rh(acac)(C_2H_4)_2]$ (**128**) (***Table 21***, entries 1-4). Significantly, lowering the rhodium catalyst loading (***Table 21***, entries 5-7) or reducing the temperature to the

lowest allowable setting on the microwave reactor of 60 ˚C led to much slower reaction rates (***Table 21***, entries 8-9).



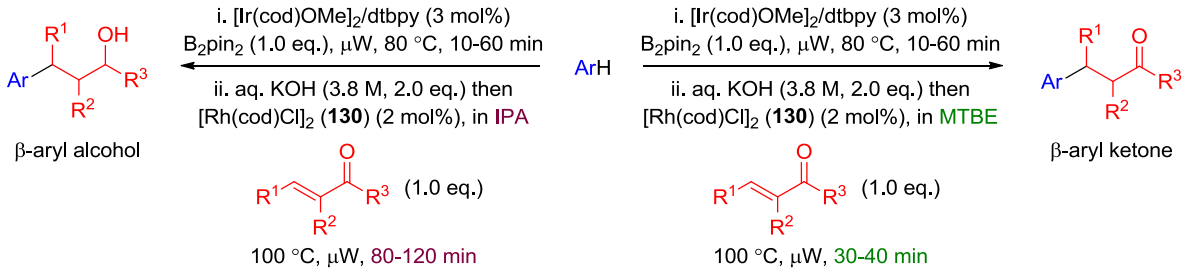
entry	Rh catalyst precursor	[Rh] (mol%)	temp. (˚C)	time (min)	LC-MS ratio 18	163	186
1	$[Rh(cod)Cl]_2$	2.0	100	30	0	27	73
2	$[Rh(cod)OH]_2$	2.0	100	30	2	30	68
3	$[Rh(nbd)Cl]_2$	2.0	100	30	12	26	62
4	$Rh(acac)(C_2H_4)_2$	2.0	100	30	42	20	38
5	$[Rh(cod)Cl]_2$	1.0	100	30	12	58	48
6	$[Rh(cod)Cl]_2$	0.5	100	30	34	39	30
7	$[Rh(cod)Cl]_2$	0.1	100	30	71	3	3
8	$[Rh(cod)Cl]_2$	2.0	60	30	46	22	31
9	$[Rh(cod)Cl]_2$	2.0	60	90	26	24	50

Table 21. Screening of rhodium catalyst precursors.

4.3.7 C-H Borylation/1,4-Conjugate Addition Sequence with $[Rh(cod)Cl]_2$ Under Schlenk and Array Conditions

With these optimised conditions identified, the general applicability of the reaction sequence was explored using a wide variety of electron-rich and electron-poor arenes and

heteroarenes with α,β-unsubstituted, α-substituted, β-substituted and cyclic α,β-unsaturated ketones (***Scheme 89***).

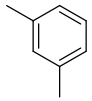
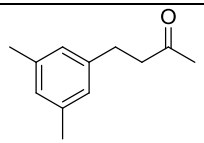
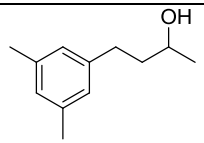
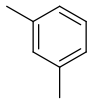
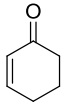
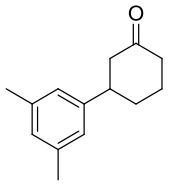
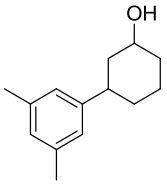
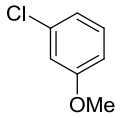
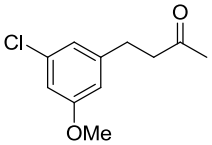
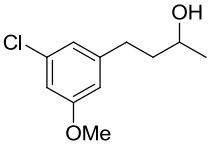
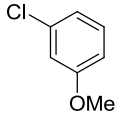
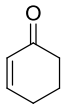
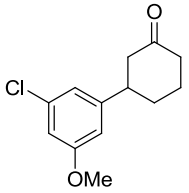
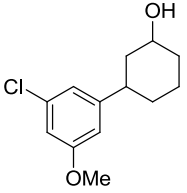
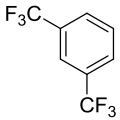
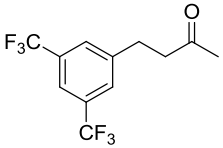
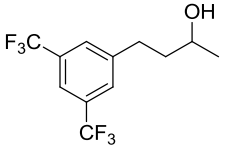


Scheme 89. Optimised one-pot C-H borylation/1,4-conjugate addition for selective access to β-arylketone or the corresponding alcohol product.

Two different batches of arene/enone combinations in 3x2 format under both reducing and non-reducing conditions were explored. In order to obtain an accurate assessment of these cascade reactions under array conditions, each reaction was first conducted independently under strict precautions to exclude oxygen using Schlenk techniques. Since for the purpose of array synthesis it would be more efficient to automate both the addition of chemicals and the purging of reactions under an inert atmosphere, the use of a Tecan Freedom Evo® liquid handling robot and a Radleys GreenHouse Parallel Synthesiser™ was explored. Similarly, an Anton Paar Synthos 3000™ microwave oven was also adopted for simultaneous heating of the reactions rather than the Personal Chemistry Emrys Optimiser™ that had been used to date, which is limited to heating one reaction at a time. Rather than focused microwave irradiation, however, the microwave oven heats with the aid of a metallic block composing of highly microwave absorbing materials. These blocks would absorb the microwave irradiation and then transfer this energy to pressure vials that are placed inside.

Attempts to use the liquid handling machine, however, were complicated by inconsistent volumes being transferred between different batches of injections. Moreover, a substantial loss of MTBE through evaporation was observed during the subsequent purging of reactions under an inert atmosphere using the greenhouse reactor. Given these practical issues it was decided that the array would simply be conducted without any precautions to exclude air, and that the addition of liquids be carried out using multi-channel pipettes. To begin the array synthesis, a preformed stock solution of the borylation catalyst, solutions of $[Rh(cod)Cl]_2$ (**130**) and the appropriate enone (MVK and cyclohex-2-enone) in degassed MTBE and a 3.8 M aqueous solution of KOH in degassed water, were first prepared under inert atmosphere using Schlenk techniques. Following additions of the iridium stock solution to individual pressure vials containing a specific arene substrate, the resultant mixtures were heated simultaneously at 80 ˚C for 1 h in the microwave oven. The pressure vessels were then opened and the seal removed. LC-MS analysis at this stage showed that all arenes underwent smooth borylation. The reaction mixtures were individually quenched with 3.8 M aqueous KOH solution and following subsequent additions of the appropriate MTBE solution of the rhodium precursor and enone, the pressure vessels were resealed and reheated in the microwave oven at 100 ˚C for a further 30 minutes. To facilitate the aqueous work-up of these multiple reaction mixtures, Biotage Isolute® phase separators containing hydrophobic frits were used. This simplified the operation to a process involving dilution of each reaction mixtures with dichloromethane and water before the phases are separated. The organic phases were then concentrated, in series, under centrifugal force on a Biotage V-10 Evaporator™ and purified by automated flash column chromatography (Flashmaster II™) using identical solvent systems. The array synthesis was subsequently repeated under

reducing conditions simply by switching the MTBE solvent in the second step for isopropanol. All these results are summarized in ***Table 22***. From the individually performed reactions, good overall isolated yields were achieved for α,β-unsubstituted and cyclic α,β-unsaturated ketones (***Table 22***, entries 1-6). Acyclic enones bearing substitution at either the α- or β-position resulted in slightly lower yields but remain within an acceptable range for a two-step synthesis (***Table 22***, entries 7-12). In each case, the remaining mass balance can be accounted for (LC-MS analysis) by unreacted ArBpin and arene arising from incomplete borylation or competing protodeboronation during the conjugate addition step. Pleasingly, all reactions repeated in air under array conditions also proceeded smoothly, albeit giving somewhat lower, but still acceptable, isolated yields. Although the reduction proceeds with low stereoselectivity, this can potentially be addressed by the addition of chiral ligands.

			non-reducing conditions				reducing conditions			
					isolated yield (%)				isolated yield % (dr)	
entry	arene	enone	product		Schlenk	array	product		Schlenk	array
1				**163**	68	45		**186**	61	46
2				**194**	65	55		**203**	58 (1:1) (*syn*:*anti*)	53 (1:1) (*syn*:*anti*)
3				**164**	71	69		**185**	71	68
4				**195**	68	63		**204**	68 (1:1.9) (*syn*:*anti*)	68 (1:2) (*syn*:*anti*)
5				**166**	53	45		**205**	53	47

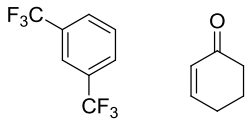
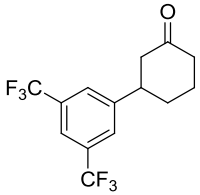
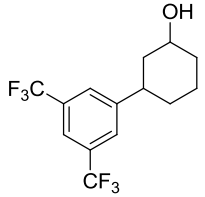
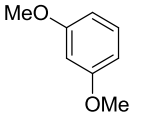
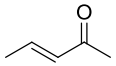
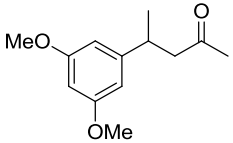
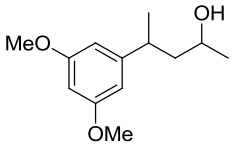
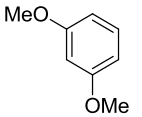
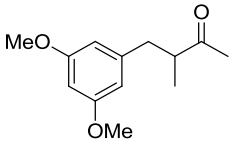
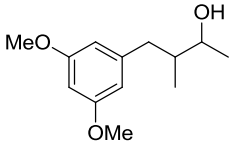
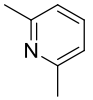
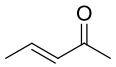
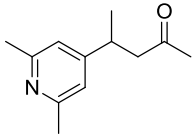
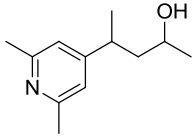
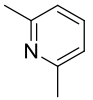
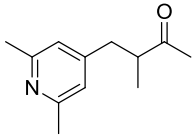
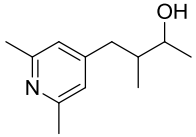
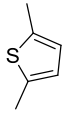
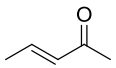
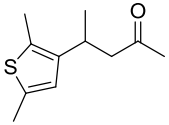
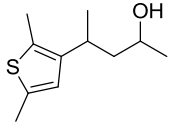
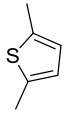
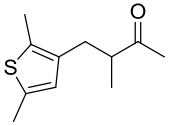
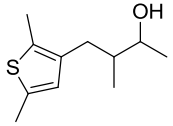
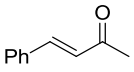
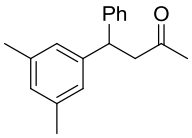
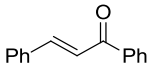
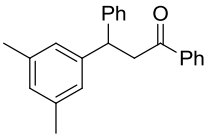
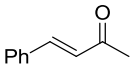
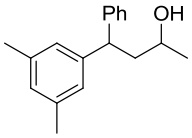
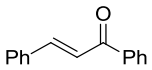
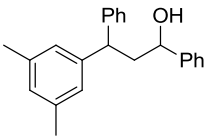
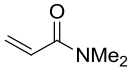
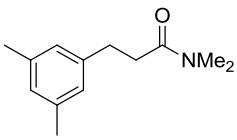
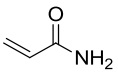
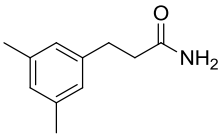
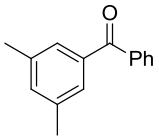
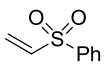
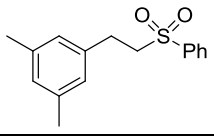
6				**196**	55	47		**206**	52 (1:1.7) (*syn*:*anti*)	44 (1:1.7) (*syn*:*anti*)
7				**197**	47	36		**207**	51 (1:1.2)	47 (1:1.2)
8				**198**	45	30		**208**	52 (1:1.3)	47 (1:1.3)
9				**199**	46	35		**209**	38 (1:1.2)	30 (1:1.3)
10				**200**	42	30		**210**	36 (1:1)	25 (1:1)
11				**201**	39	30		**211**	41 (1:1.7)	36 (1:1.7)
12				**202**	42	37		**212**	47 (1:1)	43 (1:1)

Table 22. Optimised one-pot C-H borylation/1,4-conjugate addition under Schlenk and array conditions.

4.3.8 Other Acceptors

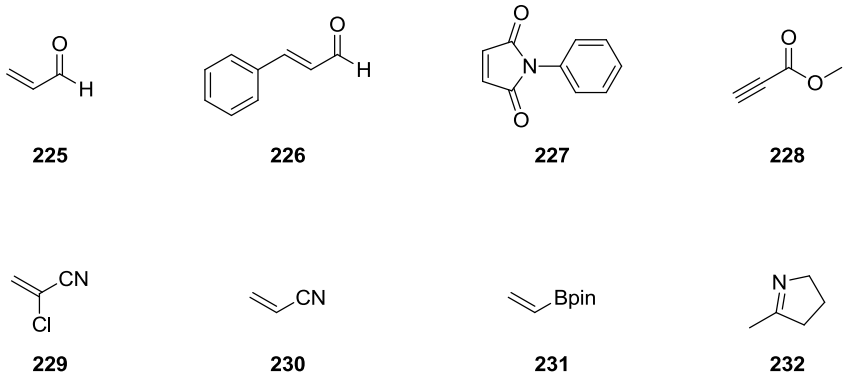
Having established an effective array protocol for the C-H borylation/1,4-conjugate addition sequence, other acceptors were screened under the non-reducing conditions (***Table 23***).

entry	acceptor		product		yield (%)
1		**190**		**191**	55[a]
2		**213**		**218**	63[b]
3		**190**		**219**	55[a]
4		**213**		**220**	61[c]
5		**214**		**221**	63[d]
6		**215**		**222**	62
7		**216**		**223**	10
8		**217**		**224**	42

[a] contain approximately 5% reduced acceptor (4-phenyl butan-2-one) by ^{1}H NMR after two purifications; [b] contain 6% of the corresponding alcohol by ^{1}H NMR after two purifications; [c] under reducing conditions – IPA solvent in step 2; [d] contain 5% oxidative Heck product after two purifications.

Table 23. Other acceptors under the C-H borylation/1,4-conjugate addition sequence.

Although phenyl-substituted enones (**190** and **213**) underwent the sequence smoothly, separation of the ketone product (**191**) from the reduced form of the acceptor (1,3-diphenylpropan-1-one and 4-phenylbutan-2-one, respectively) by flash column chromatography proved to be problematic (***Table 23***, entries 1 and 2). A similar problem was encountered under reducing conditions with the corresponding alcohol form of the acceptor as the unavoidable contaminant (***Table 23***, entries 2 and 4). Protected and unprotected α,β-unsaturated amides **214** and **215** also proceeded smoothly under non-reducing conditions, however, the purification of the amide products **221** and **222** were complicated by unavoidable co-elution of small amounts of the corresponding oxidative 'Heck' side-product (GC-MS) during flash column chromatography (***Table 23***, entries 5 and 6). Surprisingly, a small amounts of a mixture of diarylketone (**223**) and the corresponding alcohol product (GC-MS) was observed with sulfonylimine (**216**) (***Table 23***, entry 7). Although the reaction with phenylvinylsulfone (**217**) afforded the desired addition product **224** in moderate 42% yield, obtaining a pure sample of the product was complicated by the co-elution of the corresponding alcohol side-product during flash column chromatography (***Table 23***, entry 8). Disappointingly, 1,4-conjugate addition products were not observed with acrolein (**225**), *N*-phenyl maleimide (**226**) and methyl propiolate (**228**) (***Scheme 90***). Attempts to perform 1,2-additions on acrylonitrile derivatives (**229** and **230**), vinylpinacolboronate (**231**) and an imino-pyrrole derivative (**232**) were also unsuccessful.



225 **226** **227** **228**

229 **230** **231** **232**

Scheme 90. Unsuitable acceptors in the C-H borylation/addition sequence.

4.4 Conclusions

A highly robust, microwave-assisted, one-pot, tandem Ir-catalysed aromatic C-H borylation/Rh-catalysed 1,4-conjugate addition sequence, which is suitable for application in high-throughput array format, has been developed. Key to this strategy is the quenching of the borylation step prior to initiating the subsequent 1,4-conjugate addition. Both β-aryl substituted ketones and the corresponding alcohols can be selectively accessed in good overall isolated yields by employing non-reducing or reducing conditions, respectively. Mechanistic studies using deuterated methanol showed that the reduction process proceed *via* transfer hydrogenation with methanol serving as the hydrogen source. Although the reduction proceeds with low stereoselectivity, this can potentially be addressed by the addition of chiral ligands.

4.5 References

[1] King, F. D.; School, R. S. C. M. C.; 2nd ed.; Royal Society of Chemistry: Cambridge, 2002; Ch. 16; p 359-381.

[2] Holmes, D.; Chotana, G. A.; Maleczka, R. E.; Smith, M. R. *Org. Lett.* **2006**, *8*, 1407.

[3] Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792.

[4] Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

[5] Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.

[6] Shi, F.; Smith, M. R.; Maleczka, R. E. *Org. Lett.* **2006**, *8*, 1411.

[7] Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761.

[8] Kikuchi, T.; Nobuta, Y.; Umeda, J.; Yamamoto, Y.; Ishiyama, T.; Miyaura, N. *Tetrahedron* **2008**, *64*, 4967.

[9] Boebel, T. A.; Hartwig, J. F. *Tetrahedron* **2008**, *64*, 6824.

[10] Harrisson, P.; Morris, J.; Steel, P. G.; Marder, T. B. *Synlett* **2009**, 147.

[11] Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586.

[12] Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

[13] Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

[14] Ahn, K. H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178.

[15] Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175.

[16] Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275.

[17] Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503.

[18] Zhou, Q. L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467.

[19] Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755.

[20] Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879.

[21] Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699.

[22] Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645.

[23] Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

[24] Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

[25] Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

[26] Pucheault, M.; Darses, S.; Genet, J. P. *Tetrahedron Lett.* **2002**, *43*, 6155.

[27] Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

[28] Amengual, R.; Michelet, V.; Genet, J. P. *Synlett* **2002**, 1791.

[29] Yuan, W. C.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Tetrahedron Lett.* **2005**, *46*, 509.

[30] Shi, Q.; Xu, L. J.; Li, X. S.; Jia, X.; Wang, R. H.; Au-Yeung, T. T. L.; Chan, A. S. C.; Hayashi, T.; Cao, R.; Hong, M. C. *Tetrahedron Lett.* **2003**, *44*, 6505.

[31] Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934.

[32] Stemmler, R. T.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 9925.

[33] Vandyck, K.; Matthys, B.; Willen, M.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Org. Lett.* **2006**, *8*, 363.

[34] Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921.

[35] Kasak, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084.

[36] Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083.

[37] Yamamoto, Y.; Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D. G.; Miyaura, N. *Chem. Lett.* **2005**, *34*, 1224.

[38] Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D.; Yamamoto, Y.; Miyaura, N. *J. Organomet. Chem.* **2007**, *692*, 428.

[39] Martina, S. L. X.; Minnaard, A. J.; Hessen, B.; Feringa, B. L. *Tetrahedron Lett.* **2005**, *46*, 7159.

[40] Iguchi, Y.; Itooka, R.; Miyaura, N. *Synlett* **2003**, 1040.

[41] Defieber, C.; Paquin, J. F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873.

[42] Nishimura, T.; Nagaosa, M.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 860.

[43] Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.

[44] Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.

[45] Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387.

[46] Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F. X.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869.

[47] Urbaneja, L. M.; Krause, N. *Tetrahedron: Asymmetry* **2006**, *17*, 494.

[48] Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.

[49] Paquin, J. F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821.

[50] Soergel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589.

[51] Frost, C. G.; Penrose, S. D.; Lambshead, K.; Raithby, P. R.; Warren, J. E.; GleaveO, R. *Org. Lett.* **2007**, *9*, 2119.

[52] Collier, P. N. *Tetrahedron Lett.* **2009**, *50*, 3909.

[53] Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425.

[54] de la Herran, G.; Murcia, C.; Csaky, A. G. *Org. Lett.* **2005**, *7*, 5629.

[55] Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285.

[56] Navarro, C.; Moreno, A.; Csaky, A. G. *J. Org. Chem.* **2009**, *74*, 466.

[57] Chapman, C. J.; Frost, C. G. *Adv. Synth. Catal.* **2003**, *345*, 353.

[58] Navarre, L.; Darses, S.; Genet, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719.

[59] Sibi, M. P.; Tatamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571.

[60] Nishimura, T.; Wang, J.; Nagaosa, M.; Okamoto, K.; Shintani, R.; Kwong, F. Y.; Yu, W. Y.; Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464.

[61] Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450.

[62] Hayashi, T.; Tokunaga, N.; Okamoto, K.; Shintani, R. *Chem. Lett.* **2005**, *34*, 1480.

[63] Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

[64] Mauleon, P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195.

[65] Mauleon, P.; Carretero, J. C. *J. Chem. Soc., Chem. Commun.* **2005**, 4961.

[66] Mauleon, P.; Alonso, I.; Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924.

[67] Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591.

[68] Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481.

[69] Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304.

[70] Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307.

[71] Hao, X. Y.; Kuriyama, M.; Chen, Q.; Yamamoto, Y.; Yamada, K.; Tomioka, K. *Org. Lett.* **2009**, *11*, 4470.

[72] Murakami, M.; Igawa, H. *J. Chem. Soc., Chem. Commun.* **2002**, 390.

[73] Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311.

[74] Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

[75] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479.

[76] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957.

[77] Gendrineau, T.; Genet, J. P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486.

[78] Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588.

[79] Yu, X. Q.; Yamamoto, Y.; Miyaura, N. *Synlett* **2009**, 994.

[80] Iyer, P. S.; O'Malley, M. M.; Lucas, M. C. *Tetrahedron Lett.* **2007**, *48*, 4413.

[81] Mondiere, A.; Pousse, G.; Bouyssi, D.; Balme, G. *Eur. J. Org. Chem.* **2009**, 4225.

[82] Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864.

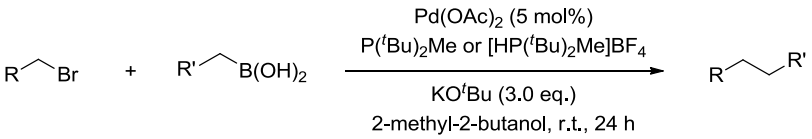
[83] Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399.

[84] Xing, C. H.; Liu, T. P.; Zheng, J. R.; Ng, J.; Esposito, M.; Hu, Q. S. *Tetrahedron Lett.* **2009**, *50*, 4953.

Chapter 5 - Alkylboronate Esters from Copper-Catalysed Borylation of Alkyl Halides and *pseudo*-Halides

5.1 Introduction

In contrast to aryl- and alkenyl boronic acids, alkylboronic acids and esters have found more limited use in organic synthesis. The major detraction in using these compounds has been their reluctance to undergo transmetalation in transition metal-catalysed cross-coupling methodologies.[1-3] Moreover, in carbon-carbon bond-forming processes such as the Suzuki-Miyaura cross-coupling reactions, the reductive elimination of R-C(sp^3) bonds are slower than R-C(sp^2) bonds, making side-reactions more likely.[1-3] Consequently, whilst the use of aryl- and alkenyl boronic acids and esters in this important carbon-carbon bond-forming strategy has become widespread, the coupling of C(sp^3) nucleophiles are still centred on the use of classical hard organometallic reagents such as alkyl-magnesium, -zinc and –lithium. These reactions are therefore fraught with poor functional group tolerance. Recently however, efficient cross-coupling of alkylboronic acids and esters, particularly in Suzuki-Miyaura protocols, have been realised through the development of highly reactive catalyst systems (***Scheme 91***).[4]



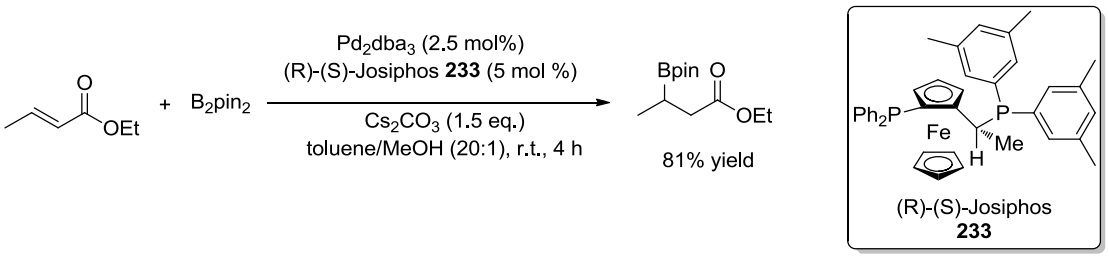
Scheme 91. Alkylboronic acids in a Suzuki-Miyaura cross-coupling reaction.

The attraction of using these organoboron C(sp^3) nucleophiles is that they are more stable, can be readily purified and have superior shelf-stability and functional group tolerance.[5,6] For these reasons, there is now a rapidly increasing demand for the development of a general

and efficient synthetic protocol for alkyl boronic acid and ester synthesis. The following section describes some of the key recent advances in this area.

5.1.1 Synthesis of Alkylboronic Acids

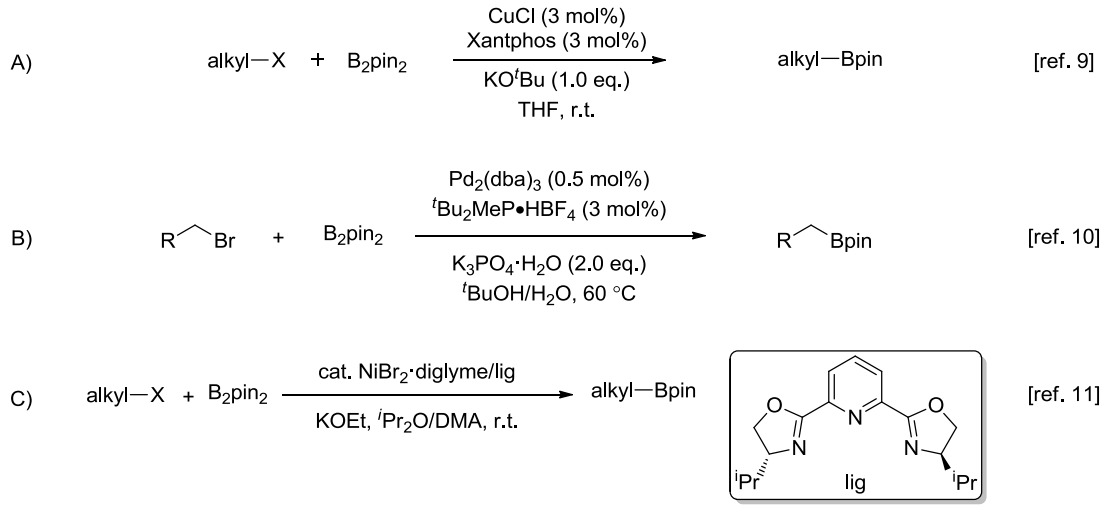
As discussed in Chapter 1, classical methods for the synthesis of alkylboronic acid derivatives involve either the hydroboration of olefins or transmetalation of alkyllithium or alkylmagnesium reagents with electrophilic boron compounds. However, these methods suffer from either poor functional group tolerance in the case of organometallic reagents, or regioselectivity issues in hydroboration. Transition-metal catalysed C-H activation also suffers from regioselectivity issues, with terminal alkyl C-H bonds favoured over the less sterically accessible internal C-H bonds. Recently, metal-catalysed β-borylation has allowed for a convenient access to enantiomerically pure carbonyl compounds containing boronate ester functionality (***Scheme 92***).[7]



Scheme 92. β-Borylation of an α,β-unsaturated carbonyl compound.

In the interest of developing a method capable of affording alkylboronate esters with a diverse range of structures and other functionalities, recent attention has been given to the

development of transition metal-catalysed methods for the activation of C-X bonds. Although such a strategy using palladium catalysts has served the preparation of aryl and alkenyl boronic acids well, extending this to alkyl reagents has proven to be difficult. This is due to the slow oxidative addition of alkyl C(sp^3)-X bonds to palladium(0), which once formed, undergo β-hydride elimination in preference to the desired transmetalation step. The following section describes efforts directed at facilitating this C-X borylation process using an alternative catalyst derived from copper. Concurrent with the publication of these results,[8] Ito and co-workers reported a similar protocol for the copper-catalysed borylation of unactivated alkyl halides with a diboron reagent (***Scheme 93A***).[9] In the same year, Biscoe and Fu separately developed a palladium- (***Scheme 93B***),[10] and nickel-catalysed variant (***Scheme 93C***)[11] of this methodology, respectively.

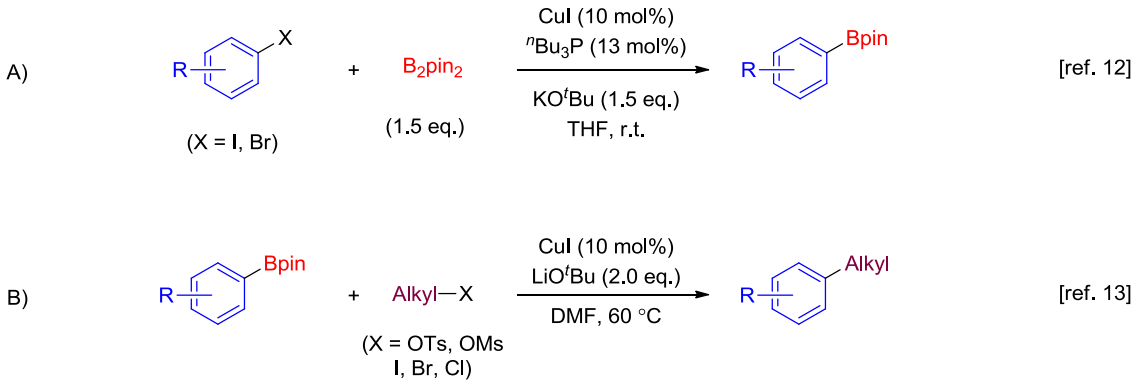


Scheme 93. Palladium-catalysed borylation of primary alkyl bromides.

5.2 Results and Discussion – Discovery, Optimisation and Scope of the Unprecedented Copper-Catalysed Borylation of Alkyl Halides

5.2.1 The Discovery of the Copper-Catalysed Borylation of Alkyl Halides

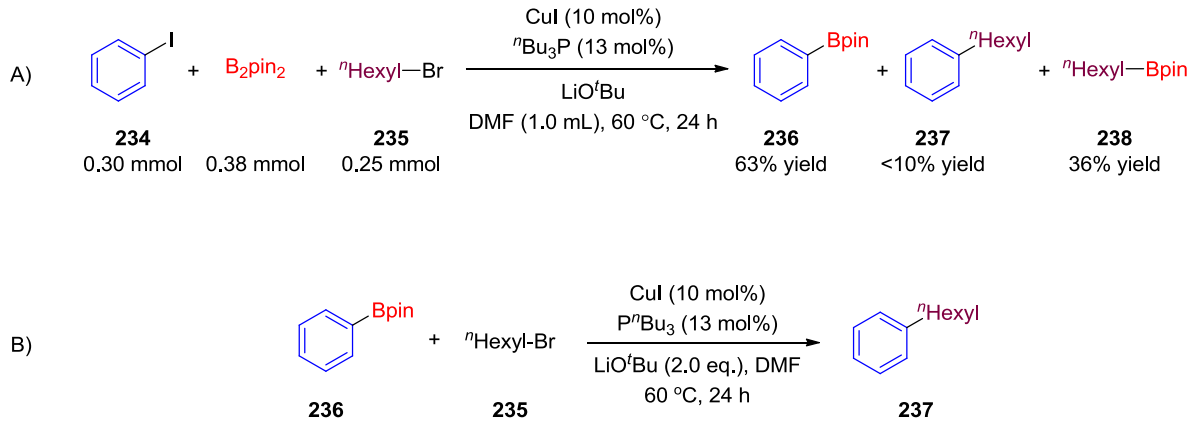
In 2009, Marder *et al*. reported that CuI in the presence of phosphines can catalyse the borylation of aryl halides with diboron reagents to generate arylboronate esters (***Scheme 94A***).[12] More recently, Liu *et al.* found that under similar reaction conditions, CuI can also catalyze the cross-coupling of unactivated alkyl electrophiles with aryl boronate esters (***Scheme 94B***).[13]



Scheme 94. Marder's aryl borylation reaction and Liu's aryl-alkyl coupling reaction.

On the basis of these findings, the groups of Marder, Liu and Steel formed a collaboration to explore the feasibility of combining both methods into a one-pot borylation/cross-coupling reaction. It was proposed that by subjecting an aryl halide, a boron electrophile, and an alkyl halide to the copper conditions in the same reaction vessel, an initial borylation of the aryl halide would take place followed by a subsequent cross-coupling reaction with the alkyl

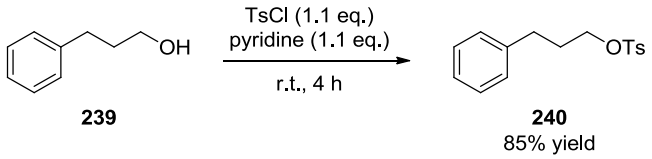
halide to give the corresponding arylalkane product. In an initial attempt to do this workers in Liu's group reacted iodobenzene (**234**), B_2pin_2 and hexyl bromide (**235**) in the presence of CuI and $^nBu_3P$ (***Scheme 95A***). Although all three reagents were consumed rapidly in the reaction and phenylBpin (**236**) was generated as anticipated, only a small amount of the cross-coupled product, phenylhexane (**237**) was obtained. A thorough analysis of the reaction mixture then revealed that an alkylboronate ester hexylBpin (**238**)**,** was produced in 36% isolated yield. In an independent experiment, Liu's group was able to confirm that phenylBpin (**236**) reacts with hexylbromide (**235**) to produce the cross-coupled arylalkane (**237**) under the same reaction conditions (***Scheme 95B***). All of these observations indicated that the alkyl halide must be consumed by an alternative pathway that is faster than its reaction with the *in-situ* formed arylboronate ester (**236**).



Scheme 95. Initial attempt to develop a one-pot borylation/cross-coupling reaction.

In the presence of a strong base such as LiO^tBu, it was conceivable that a competing elimination process may be involved, and that the hexene side-product is too volatile under GC-MS detection. To explore this possibility, a less volatile electrophile, 3-

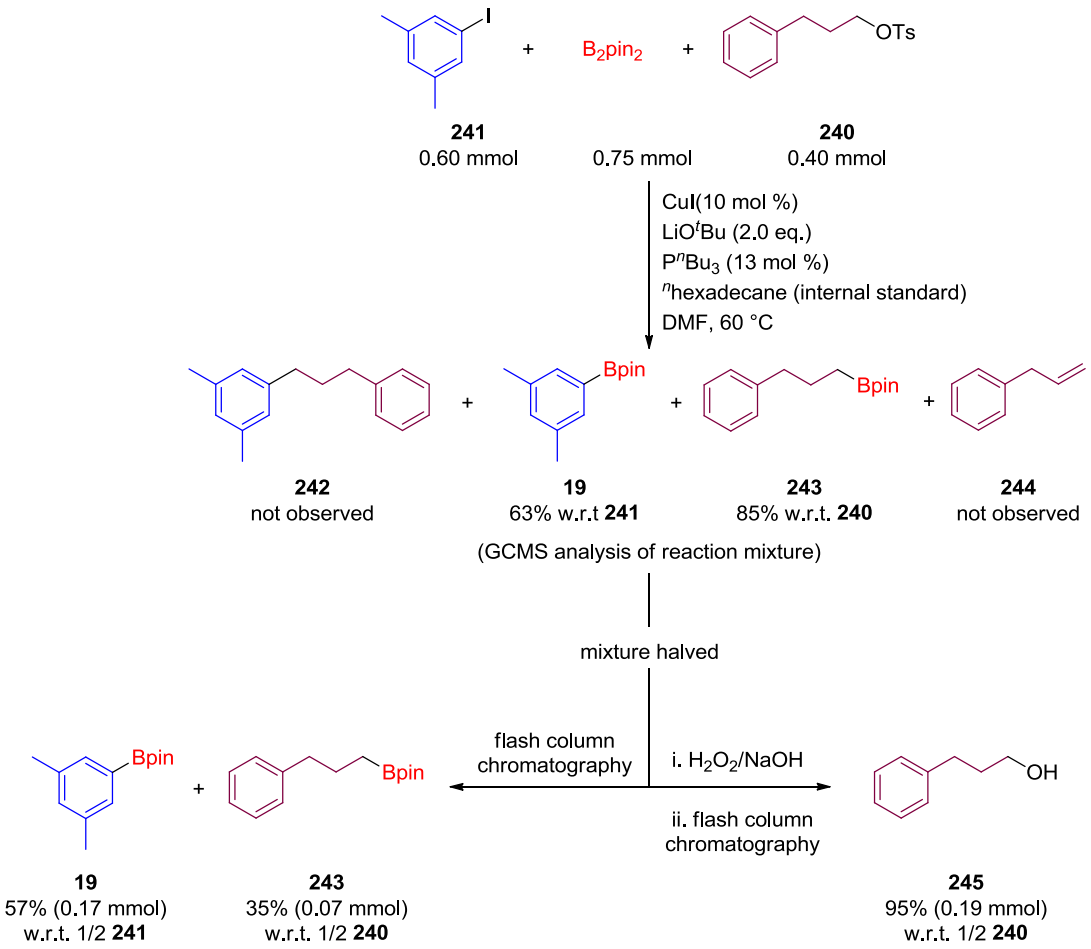
phenylpropyltosylate was first prepared by treating 3-phenylpropanol (**239**) with tosyl chloride in presence of pyridine (***Scheme 96***).



239 **240**
85% yield

Scheme 96. Preparation of 3-phenylpropyltosylate.

With 3-phenylpropyltosylate (**240**) in hand, this electrophile was subjected to the 'one-pot' conditions with iodobenzene (**234**) replaced with 3,5-dimethyliodobenzene (**241**) (***Scheme 97***). Analysis of the reaction mixture *in-situ* by GC-MS using ^{n}hexadecane as an internal standard, revealed that the alkylboronate **243** was produced in 85% yield, accompanied by smaller amounts of the aryl boronate **19** (63%). More importantly, the elimination side-product **244** was not observed. This suggested that the lower yields in the initial experiment resulted from losses during isolation. Consistent with this, when half of the reaction mixture was purified, only 35% isolated yield of alkyl boronate ester **243** was obtained (based on half the amount of aryl iodide used in the first step). However, 95% of the corresponding alcohol **245** was obtained following oxidation of the remaining reaction mixture.

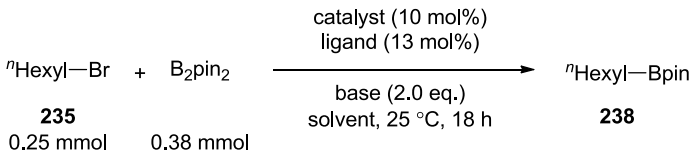


Scheme 97. Investigating the mass balance from the one-pot borylation/cross-coupling reaction.

All of these results suggested that the unprecedented copper-catalysed cross-coupling reaction between the alkyl halide and diboron reagent is far more efficient than previously indicated in ***Scheme 95A***.

5.2.2 Optimisation Efforts

Following these results, efforts were subsequently directed to optimising this copper-catalysed borylation of hexyl bromide (***Table 24***). This work was largely undertaken by Yang, Zhang, Wu, Liang, Liu and Fu of Liu's group with the key results independently verified by the author and Czyzewska of Steel and Marder's groups, albeit with slightly lower isolated yield. This was attributed to a greater loss of materials during flash column chromatography arising from a different grade of silica used. From a range of copper salt, ligand, base and solvent screened, the desired alkylboronate ester **239** was obtained in optimum 84% yield at 25 ˚C in 18 hours using a combination of CuI as catalyst precursor, PPh_3 as ligand, LiOMe as base and DMF as solvent (***Table 24***, entry 6). In addition to B_2pin_2, other diboron reagents such as bis(neopentyl glycolato)diboron (B_2neop_2) function equally effectively (***Table 24***, entry 15). The necessity for copper in these reactions was confirmed by the observation that without adding the catalyst the reaction does not occur (***Table 24***, entry 21). Moreover, the possible involvement of palladium or nickel contamination in the catalyst was largely eliminated by the observation that palladium and nickel salts provide only a trace amount of hexylBpin (**238**) under the optimised reaction conditions (***Table 24***, entries 19-20). The role of other more effective palladium or nickel contaminants in these reactions, however, cannot be entirely ruled out. Finally, the reaction is not significantly sensitive to moisture, because the addition of 4.0 equivalents of water only reduces the yield to 77% (***Table 24***, entry 22).

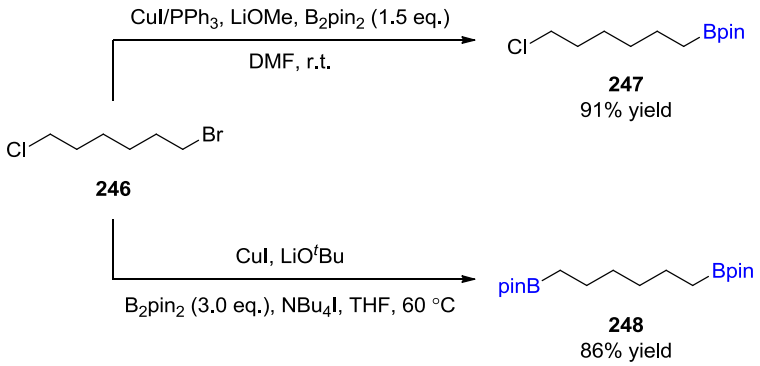


entry	catalyst	ligand	base	solvent	temp (˚C)	yield **238** (%)[a]
1	CuI	PPh_3	LiO^tBu	DMF	25	84
2	CuI	PPh_3	KO^tBu	DMF	25	28
3	CuI	PPh_3	NaO^tBu	DMF	25	24
4	CuI	PPh_3	LiHMDS	DMF	25	13
5	CuI	PPh_3	Li_2CO_3	DMF	25	Trace
6	**CuI**	**PPh_3**	**LiOMe**	**DMF**	**25**	**91(89[i])**
7	CuI	P$^nBu_3$	LiOMe	DMF	25	78
8	CuI	P$^tBu_3$	LiOMe	DMF	25	70
9	CuI	1,10-phen	LiOMe	DMF	25	65
10	CuBr	PPh_3	LiOMe	DMF	25	72
11	CuCl	PPh_3	LiOMe	DMF	25	56
12	$Cu(OTf)_2$	PPh_3	LiOMe	DMF	25	60
13	CuI	PPh_3	LiOMe	DMSO	25	57
14	CuI	PPh_3	LiOMe	THF	25	35
15[b]	CuI	PPh_3	LiOMe	DMF	25	87(83[i])
16[c]	CuI	/	LiO^tBu	THF	25	90
17[d]	CuI	/	LiO^tBu	THF	60	86
18[e]	CuI	/	LiO^tBu	MeCN	60	76
19[f]	$Pd(OAc)_2$	PPh_3	LiOMe	DMF	25	Trace
20[g]	NiI_2	PPh_3	LiOMe	DMF	25	Trace
21	-	PPh_3	LiOMe	DMF	25	Trace
22[h]	CuI	PPh_3	LiOMe	DMF	25	77

[a] GC yields after 18 hours (average of two runs); [b] bis(neopentyl glycolato)diboron was used in the coupling; [c] ^{n}hexyl iodide was used; [d] ^{n}hexyl chloride was used and 1.0 eq. of $N(Bu)_4I$ was added; [e] ^{n}hexyl tosylate was used and 1.0 eq. of $N(Bu)_4I$ was added; [f] 2 mol% of Pd catalyst used; [g] 2 mol% of anhydrous NiI_2 used - similar negative results were obtained with $NiCl_2$•$6H_2O$ and $NiBr_2$•$3H_2O$; [h] 18 μL (1.0 mmol) of water was added; [i] isolated yield.

Table 24. Optimisation of the copper-catalysed borylation of hexyl bromide.

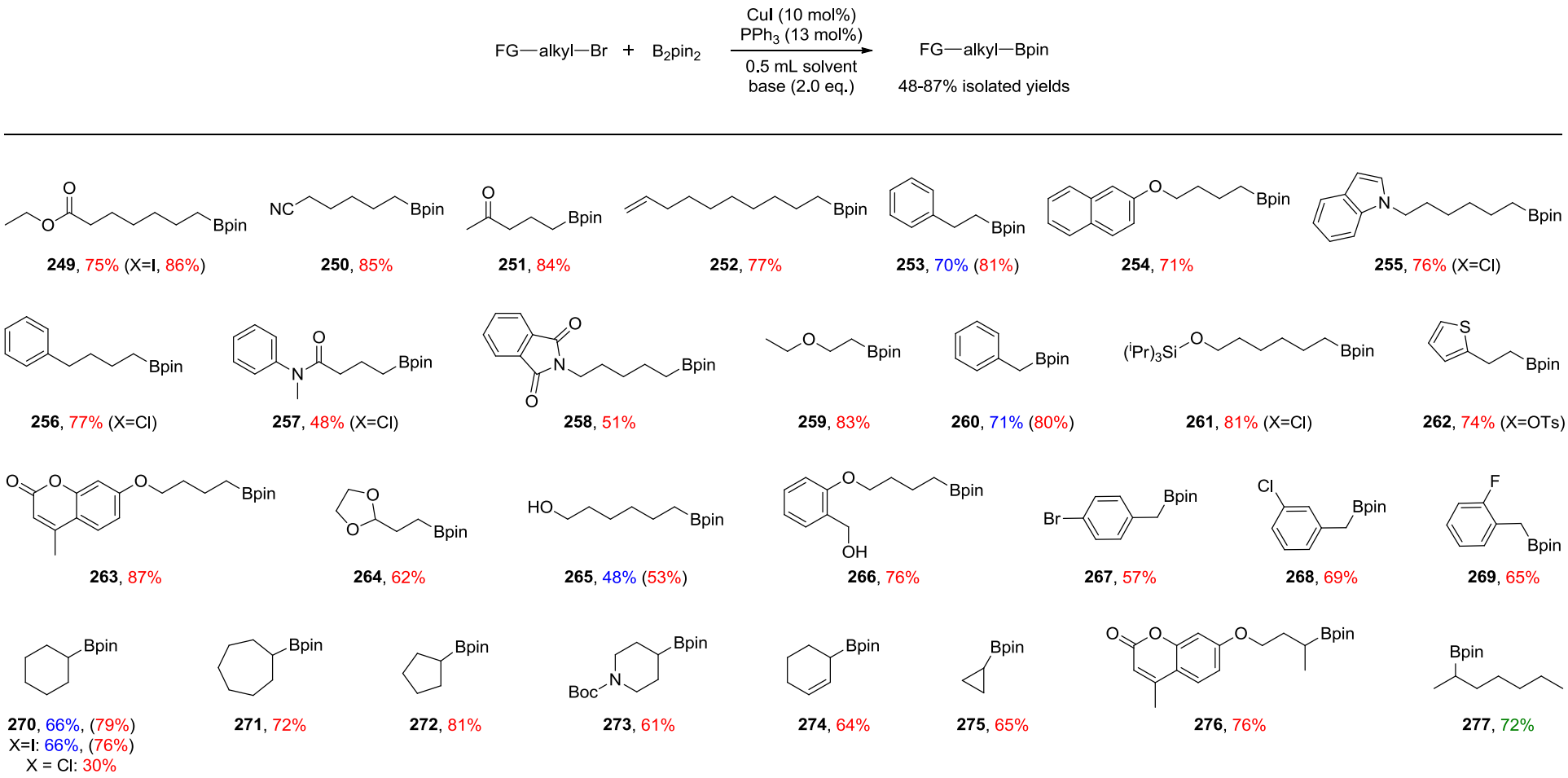
^{n}Hexyl iodide, chloride, and tosylate are also viable substrates with optimal yields of 90%, 86%, and 76%, respectively (***Table 24***, entries 16-18). However, higher temperatures (60 ˚C) and the addition of (Bu_4N)I are required for reaction of the chloride and tosylate. Presumably, these proceed *via* the iodide and, interestingly, for this substrate the PPh_3 ligand is not needed but the optimal base changes from LiOMe to LiO^{t}Bu. Overall, the reactivity decreases in the order: iodide > bromide > chloride ≈ tosylate (***Table 24***, entries 16-18). This observation is consistent with the previous Cu-catalyzed coupling of Grignard or organoboron[12] reagents with alkyl electrophiles.[12,14] This reactivity difference can be exploited to allow the selective substitution of the bromine atom of 6-chlorohexyl bromide (**246**) at room temperature affording monoborylated product **247** in an excellent 91% yield (***Scheme 98***). However, on increasing the reaction temperature to 60 ^{o}C, and in the presence of Bu_4NI, both bromide and chloride react efficiently to give bisborylated product **248**.



Scheme 98. Site-selective borylation.

5.2.3 Substrate Scope

With optimised conditions identified, the scope of the new borylation reaction was examined (***Scheme 99***). The yields in red were obtained by Zhang, Yang, Wu, Liang, Liu and Fu of Liu's group while the yields in blue and green were obtained by the author and Czyzewska, respectively. Consistent with the previous observation in ***Table 24***, entry 6, slightly lower isolated yields were obtained by the author when compared to those obtained by Liu's group. From these studies, many synthetically important functional groups including ester (**249**), cyano (**250**), ketone (**251**), ether (**254** and), olefin (**252**), amide (**257** and **258**), ketal (**264**), and silyl ether (**261**) were well tolerated in the reaction with the isolated yields of the desired alkylboronates ranging from about 50% to 80%. Furthermore, arene (**253**, **254**, **256** and **260**) and heterocycle-containing compounds (**263**, **255** and **262**) are good substrates for the borylation process. Significantly, even the presence of a free alcohol group (**265** and **266**) does not interfere with the reaction. This feature compares favorably with early alkylboronate syntheses starting from alkyllithium or alkylmagnesium reagents, in which nearly all of the alkyl groups are only hydrocarbons.[15,16] More reactive electrophiles such as benzyl bromides (**35-37**)[12,17] can be readily borylated by this method. However, 2.0 eq. of the diboron reagent was required to minimise the formation of bibenzyl. Finally, it was confirmed that aryl halides are less reactive than alkyl halides (**267-269**). This allows alkylhalides bearing bromo and chloro substituted arene rings to be successfully used, potentially allowing for subsequent modifications through further coupling reactions at the halogenated positions.

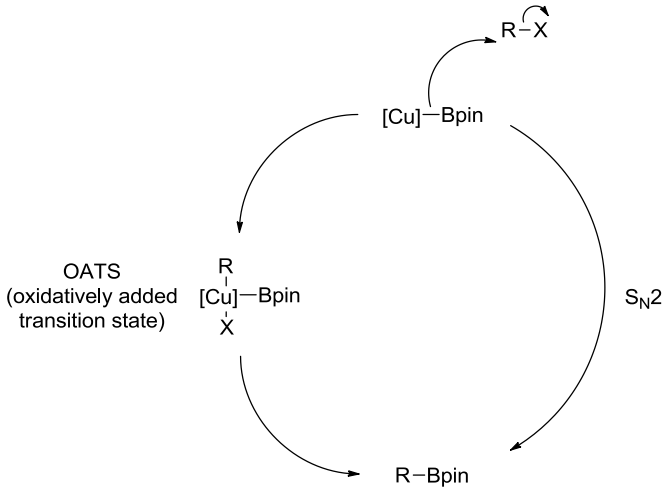


Scheme 99. Substrate scope of the borylation reaction.

In addition to primary alkyl electrophiles, secondary alkyl halides can also be borylated. For cyclohexyl bromide, the yield reaches 50% at 25 ^{o}C in 24 hours. Simply increasing the reaction temperature to 37 ^{o}C enables the desired secondary alkylboronate **270** to be produced in a 66% isolated yield. In a similar fashion, other cyclic and acyclic secondary bromides can be smoothly borylated (**271-277**). A similar reactivity profile to primary halides is observed; cyclohexyl iodide is readily converted to **270** (yield = 66% yield), whilst cyclohexyl chloride affords only a moderate yield (30%) under the current conditions. It is important to note that in most of the previous Cu-catalyzed cross-coupling of organometallic reagents with an aliphatic electrophile, secondary alkyl halides have seldomly been used successfully.[13,18-20] This new borylation reaction therefore provides an interesting option for Cu-catalyzed cross-coupling reactions of secondary alkyl electrophiles. Moreover, Czyzewska showed that commercial polystyrene-bound PPh_3 can be employed in the reaction with no loss in efficiency. For example, borylation of 2-bromoheptane led to a crude product mixture which required two chromatographic runs to separate the heptyl-2-Bpin product **277** from PPh_3. With PS-PPh_3 clean formation of the product and no separation problems were encountered affording **277** in 72% yield.

5.3 Results and Discussion - Mechanistic Studies

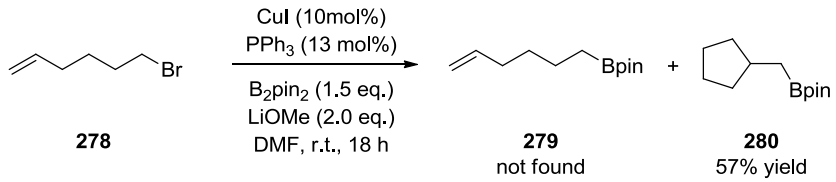
The copper-catalyzed borylation of alkyl electrophiles above represents a new and exciting route towards alkyl boronate esters. The mechanism of this transformation, however, is not immediately obvious. In analogy to the copper-catalysed cross-coupling of aliphatic electrophiles,[13,14,18-20] the mechanism of the present borylation reaction might involve an S_N2-type substitution with a Cu(I) boryl complex[21,22] generated through transmetalation[12] between Cu(I) and B_2pin_2 (***Scheme 100***). Alternatively, the alkyl halide might interact with the Cu(I) boryl complex *via* an oxidatively added transition state (OATS) similar to that proposed for the Cu-catalyzed borylation of aryl halides.[12] However, hydroxyl group compatibility and the selective reaction at an alkyl sp^3 C-X bond over an aromatic sp^2 C-X bond are inconsistent with the catalytic cycle proposed for the borylation of aryl halides. The following section describes efforts directed towards obtaining further insights into the mechanistic pathway involved in this transformation.



Scheme 100. Possible mechanisms for C-X activation *via* a copper-boryl complex.

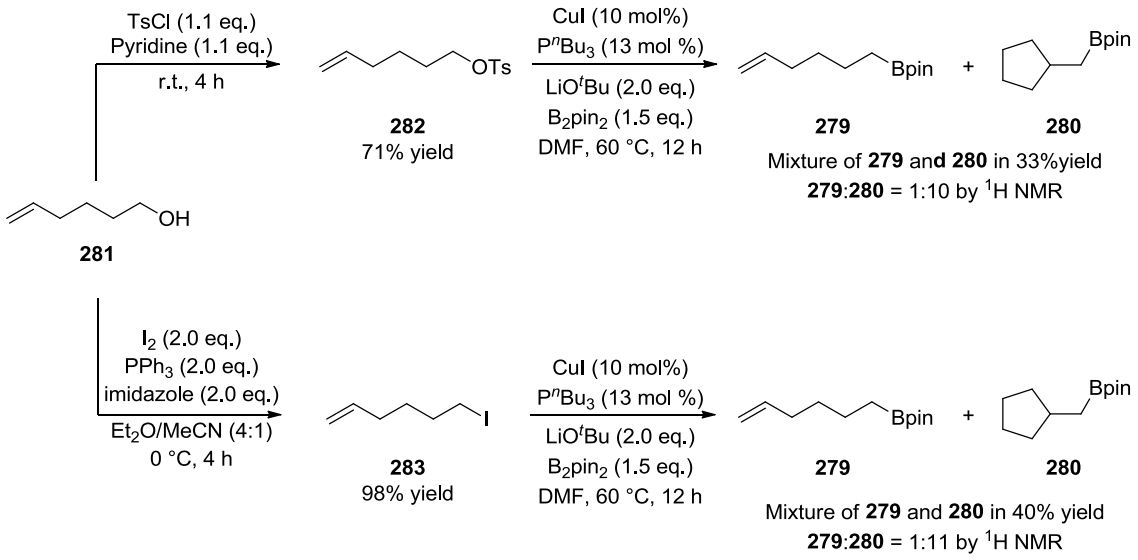
5.3.1 Borylation of 6-bromohex-1-ene

Whereas the borylation of 10-bromo-dec-1-ene proceeds smoothly to give **252** as expected (***Scheme 99***), the borylation of thye analogous 6-bromohex-1-ene (**278**) affords cyclopentylmethyBpin (**280**) (***Scheme 101)***. This combined with the absence of the linear 5-hexenylBpin (**279**), suggests a radical mediated pathway is involved. This result was subsequently confirmed by workers in Liu's group.



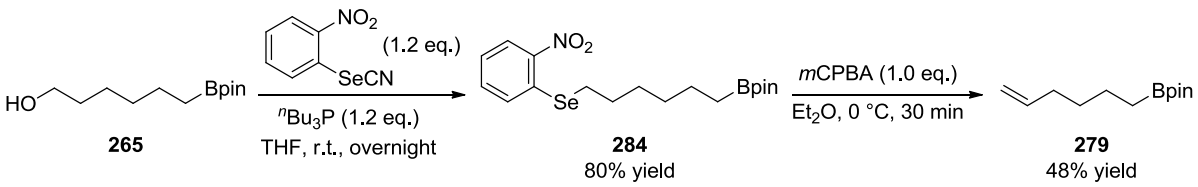
Scheme 101. Borylation of 6-bromohex-1-ene.

Similar observations were made with the tosylate and iodide analogues **281** and **282**, prepared from the corresponding alcohol (**261**) under the classic tosylation and Appel conditions (***Scheme 102***).



Scheme 102. Borylation of hex-5-en-1yl 4-methylbenzenesulfonate and 6-iodohex-1-ene.

These results suggest that the cyclopentylmethylBpin (**280**) may have been generated *via* a copper-catalysed cyclisation of an initially formed linear 5-hexenylBpin (**279**). However, by monitoring these experiments by ^{1}H NMR spectroscopy the product ratio **279**:**280** was maintained throughout the course of both reactions suggesting that **280** is not formed *via* **279**. To confirm this an authentic sample of **279** was required. An initial attempt to prepare this 5-hexenylBpin from the corresponding Grignard reagent generated from 5-hexenylbromide was unsuccessful. However, the desired 5-hexenylBpin (**279**) was finally prepared *via* oxidation of the selenide **281**, which was generated from the reaction of **265** with *o*-nitrophenylselenocyanate, with *m*CPBA (***Scheme 103***).

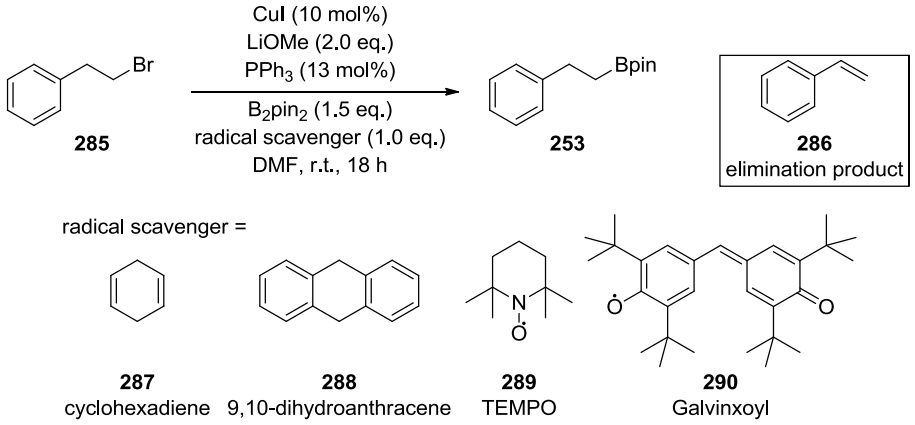


Scheme 103. Synthesis of 6-Bpin-hex-1-ene *via* a selenide intermediate.

With 5-hexenylBpin (**279**) in hand, this compound was subjected to the copper-catalysed borylation conditions in deuterated dimethylformamide and monitored by ^{1}H NMR spectroscopy (***Scheme 98A***). However, no reaction could be observed after 12 hours at 60 ˚C suggesting that cyclopentylmethylBpin (**280**) could not have formed from 5-hexenylBpin (**279**) in the borylation of 6-bromohex-1-ene (**278**).

5.3.2 Radical Scavenger Experiments

To test the hypothesis that a radical-mediated pathway is involved, the borylation of phenylethylbromide (**285**) was performed in the presence of a range of radical scavengers (***Table 25***). The reaction proceeded smoothly with cyclohexadiene (**287**) as the radical scavenger (***Table 25***, entry 2) and again this was independently confirmed in Liu's group using cyclohexylbromide and ^{n}hexylbromide as electrophiles.[8] The related radical scavenger 9,10-dihydroanthracene (**288**) also afforded similar result (***Table 25***, entry 3). An attempt to use TEMPO (**289**) was complicated by its oxidising nature leading to a complex mixture of products (***Table 25***, entry 4). However, the use of Galvinoxyl (**290**) resulted in complete inhibition of the borylation reaction leading to the exclusive formation of styrene (**286**) (***Table 25***, entry 5).

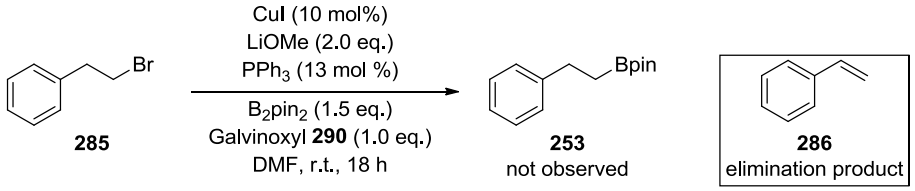


entry	radical scavenger	GC-MS analysis	isolated yield (%)
1	none	100% conversion	**253** (66)
2	**287**	100% conversion	**253** (57)
3	**288**	100% conversion	**253** (61)
4	**289**	complex mixture	not isolated
5	**290**	formation of **286** observed[a]	**286** (65%)

[a] A trace amount of Galvinoxyl-Bpin was also detected

Table 25. Borylation of phenylethylbromide in presence of radical scavengers.

In order to confirm that Galvinoxyl (**290**) was acting as a suitable radical scavenger, various modifications of the reaction conditions were explored (***Table 26***). In reactions where both B_2pin_2 and Galvinoxyl are present, a trace amount of a Galvinoxyl-Bpin adduct (not isolated) was observed by GC-MS analysis (*m*/*z* = 548) (***Table 26***, entries 1, 3, 5 and 6). No background reactions involving Galvinoxyl and any of the other components of the borylation reaction could be readily identifiable. It is interesting, however, that the elimination reaction appears to require Galvinoxyl in the presence of both B_2pin_2 and LiOMe (compare entries 1 and 6). One possible explanation is that a Galvinoxyl-B_2pin_2 or Galvinoxyl–Bpin adduct was formed which then inhibits the methoxide base from forming a boron'ate' complex with B_2pin_2. The unreacted base is then able to promote E2 elimination of HBr and afford the observed alkene.



entry	R-X	CuI	PPh_3	B_2pin_2	LiOMe	Galvinoxyl-Bpin in crude mixture	isolated yield (%) **253**	isolated yield (%) **286**
1	✓	✓	✓	✓	✓	trace	0	65
2	✓	×	×	×	×	-	-	-
3	✓	✓	✓	✓	×	trace	0[a]	0
4	✓	×	×	×	✓	-	0	60
5	✓	×	×	✓	✓	trace	0	61
6	×	✓	✓	✓	✓	trace	0	0
7[b]	✓	×	✓	✓	✓	-	0	0

[a] 88% of phenylethylbromide **285** was recovered; [b] reaction was carried out in absence of Galvinoxyl.

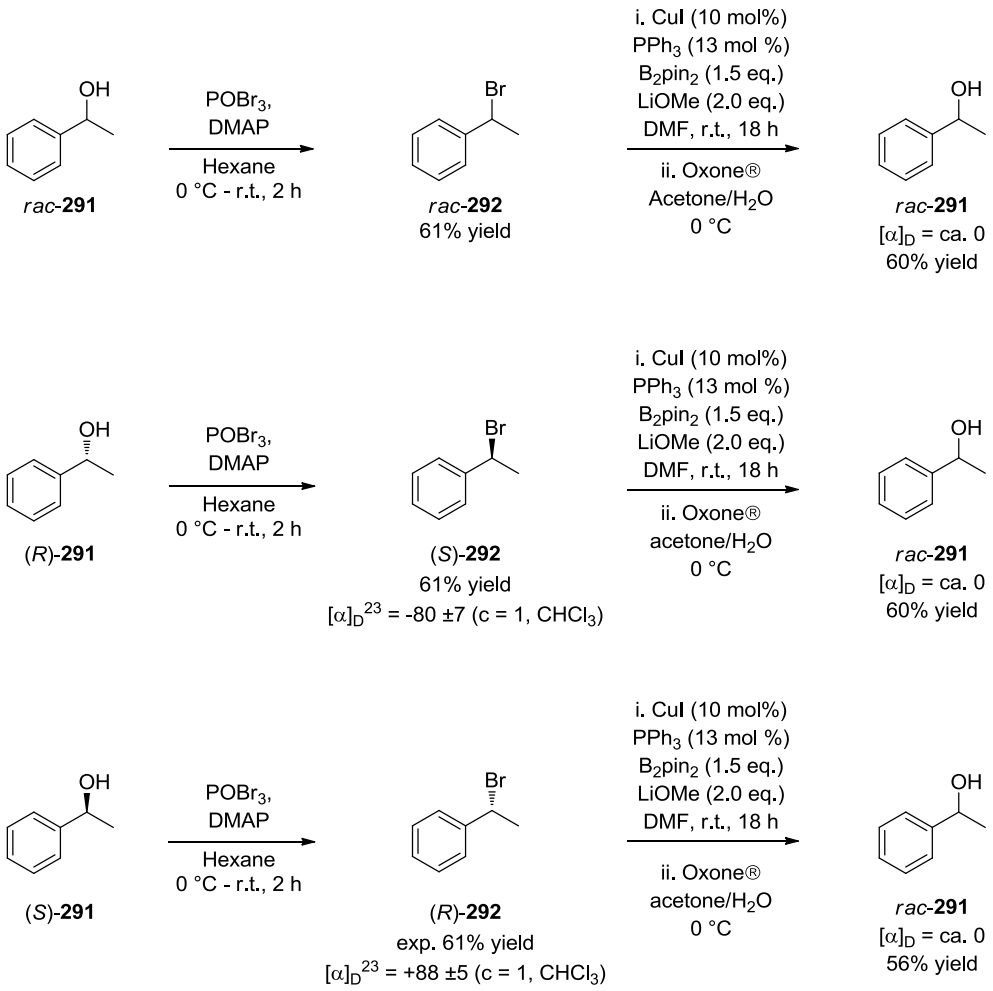
Table 26. Evaluation of Galvinoxyl as a suitable radical scavenger.

These observations provide doubts as to the validity of Galvinoxyl acting as a radical scavenger under the tested conditions.

5.3.3 Borylation of Enantiomerically Pure Substrates

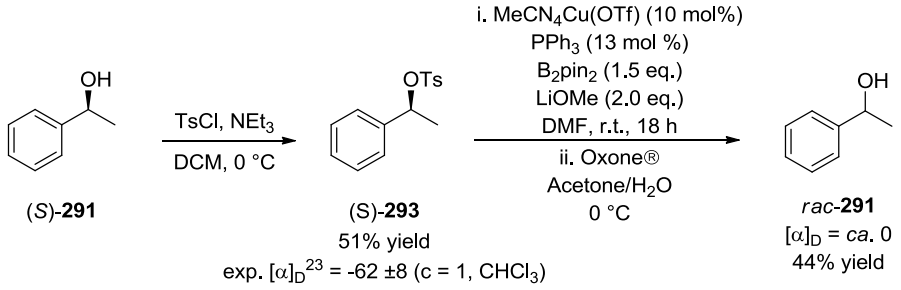
To further investigate the putative involvement of radicals, borylation of enantiomerically and diastereomerically pure substrates were undertaken. Scrambling would be expected to occur if a free-radical mechanism was involved. The work in this area was carried out on 1-phenylethanol derivatives. An initial attempt to prepare the racemic (1-bromoethyl)benzenes (*rac*-**289**) from racemic 1-phenylethanol (*rac*-**288**) using tetrabromomethane under the classic Appel conditions was unsuccessful due to unavoidable

co-elution of the $CHBr_3$ by-product during flash column chromatography. The required bromide was finally achieved using phosphorous oxybromide, with the product readily identified by the bromine isotope pattern in mass spectrometry (*m*/*z* = 184 and 186). The enantiomerically pure bromide analogues were subsequently prepared from the corresponding 1-phenylethanol enantiomers under the same conditions. Subsequent $[\alpha]_D$ measurements of these products showed relatively equal but opposite optical rotation, confirming that their stereochemistry had not been lost. Standard conditions were employed in the subsequent borylation reaction, followed by one-pot oxidation to alcohol using an aqueous solution of Oxone® (***Scheme 104***). Significantly, $[\alpha]_D$ measurements of the oxidised alcohol products **288** showed that the borylation/oxidation of both (R) and (S) enantiomers of (1-bromoethyl)benzene (**289**) afforded the same racemic mixture of alcohols as from racemic bromide (*rac*-**289**).



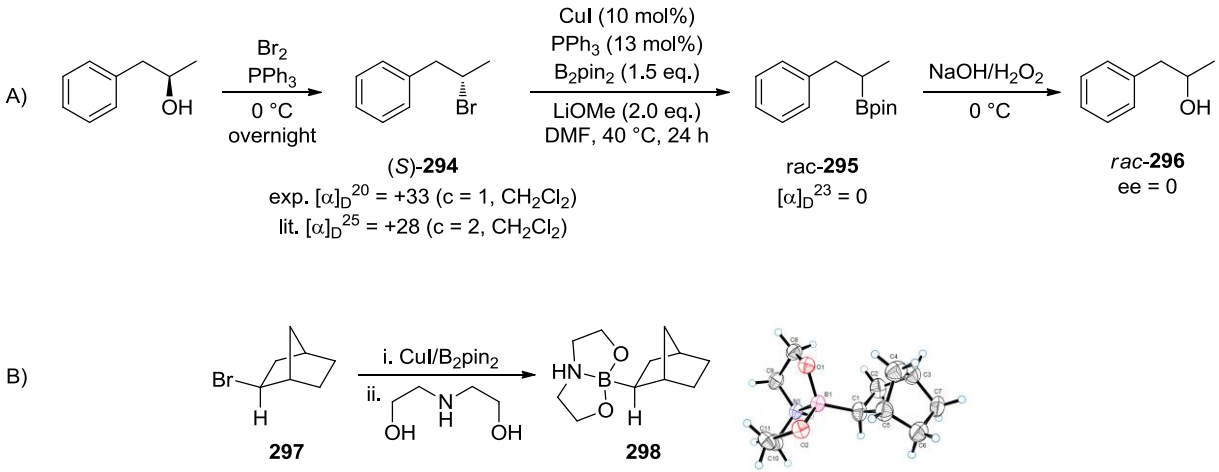
Scheme 104. Loss of stereochemistry in the borylation/oxidation sequence on bromo derivatives of 1-phenyl ethanol.

To rule out the possibility of halide-mediated scrambling of the stereochemistry, borylation of the enantiomerically pure tosylate analogue 1-phenylethyl 4-methylbenzenesulfonate [(S)-**290**], using $Cu(MeCN)_4(OTf)$ as the catalyst, was undertaken. Again, consistent with a radical pathway complete loss of stereochemistry was observed (***Scheme 105***).



Scheme 105. The loss of stereochemistry in the borylation of 1-phenylethyl 4-methylbenzenesulfonate.

Concurrent with these studies, workers in Liu's group reported similar observation starting from the analogous (S)-(2-bromopropyl)benzene [(S)-**294**)] (***Scheme 106A***). Interestingly, they also reported that the borylation of *exo*-2-bromonorbornane (**297**) proceeds with retention of configuration to give *exo*-2-B(OR)$_2$norbornane (**298**) (***Scheme 106B***).

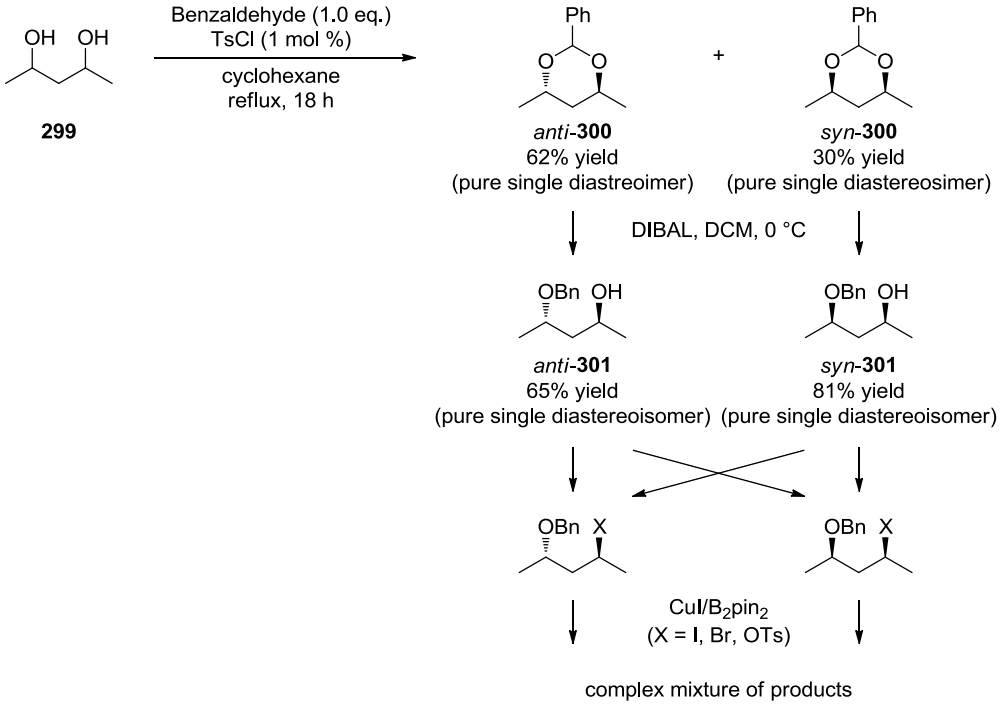


Scheme 106. Loss and retention of stereochemistry in the borylation reaction, as reported by workers in Liu's group.

This observation, however, does not rule-out involvement of radicals as trapping of a norbornyl radical intermediate is expected to occur from the less hindered *exo* face.

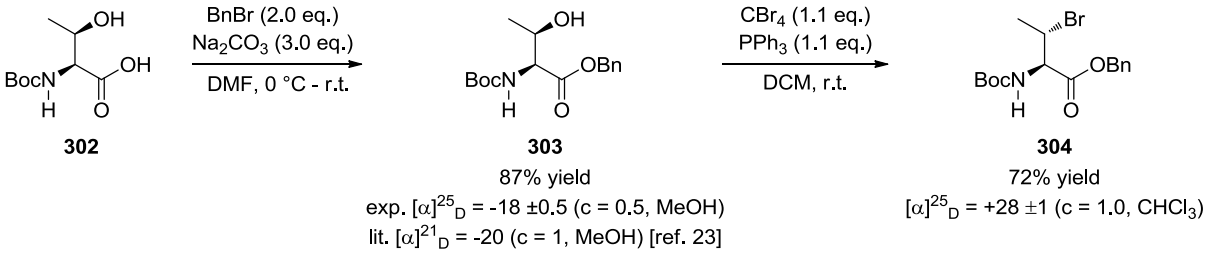
5.3.4 Borylation of Diastereomerically Pure Substrates

Concurrent with the studies described above, alternative stereochemical probe substrates were explored. Pure *syn* and *anti* monoprotected 2,4-pentanediols (**301**), synthesised *via* a DIBAL reduction of the corresponding acetal (**300**), were transformed into the relevant alkyl electrophiles (alkyl-iodide, -bromide and –tosylate) (***Scheme 107***). For reasons not yet fully understood, the attempted borylation of all these substrates afforded a complex and intractable mixture of products.



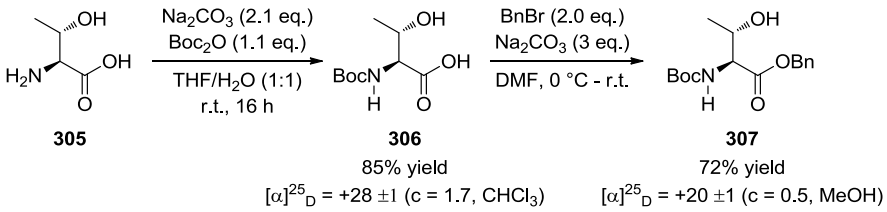
Scheme 107. Synthesis and borylation of diastereomerically pure substrates.

Following these results, threonine derivatives were considered as alternative stereochemical probes. Conveniently, the stereochemical properties of these compounds are well-documented in the literature simplifying the downstream analysis. The synthesis of target compound **303** was realised through esterification of commercial N-Boc-L-threonine (**302**). The retention of stereochemistry of **299** was confirmed by an almost identical $[\alpha]_D$ value when compared to the literature.[23] The subsequent Appel reaction proceeded smoothly to afford the bromo derivative **304**, in good yield (***Scheme 108***).



Scheme 108. Synthesis of the bromo derivative of N-Boc-L-threonine benzyl ester.

It was speculated that the ^{1}H NMR spectra of the two diastereomers of N-Boc-threonine benzyl esters would be sufficiently different allowing for the diastereomeric ratios to be readily determined without having to perform chiral HPLC or $[\alpha]_D$ measurements. Consequently, **307**, the diastereomer of **302**, was synthesised through sequential protection of the amine and carboxylic acid groups of L-*allo*threonine (**305**) (***Scheme 109***).



Scheme 109. Synthesis of N-Boc-L-*allo*threonine benzyl ester.

Pleasingly, the ^{1}H NMR spectra of diastereomeric pairs **303** and **307** are distinctively different and can be readily identified in a mixture (***Figure 17***).

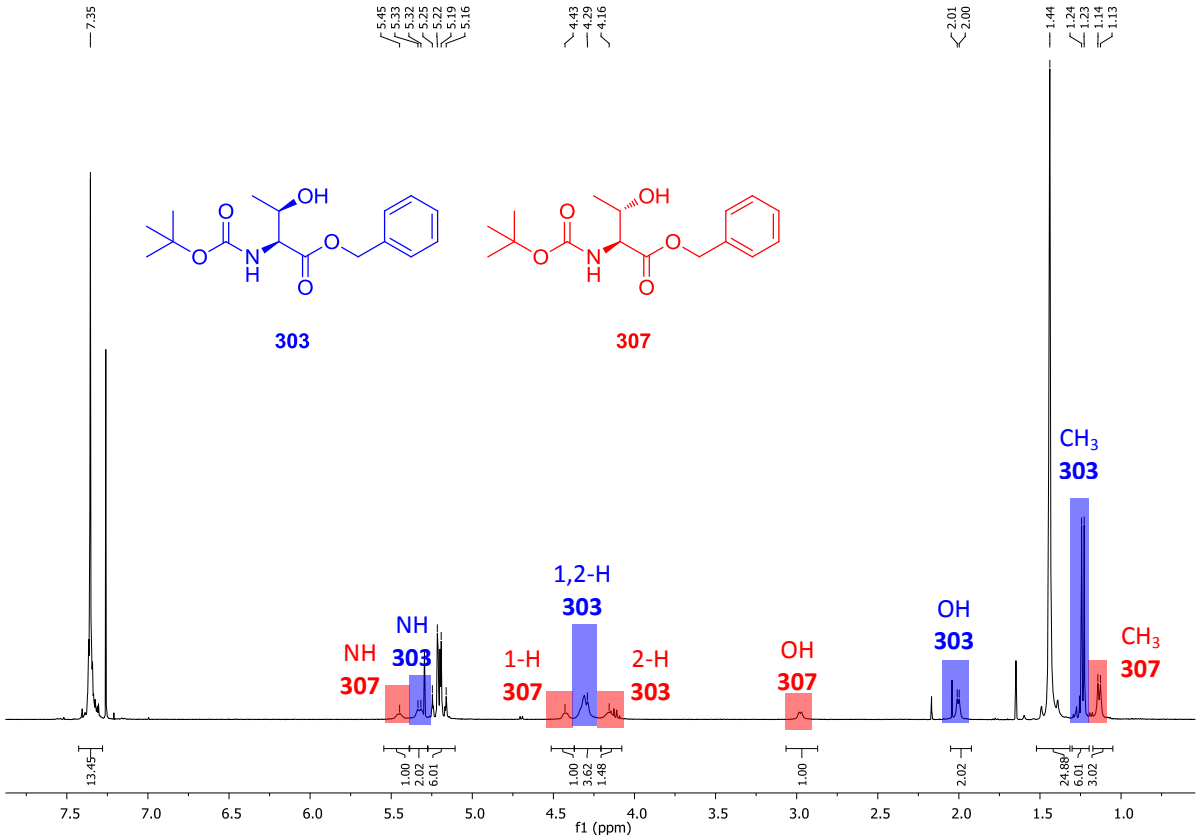
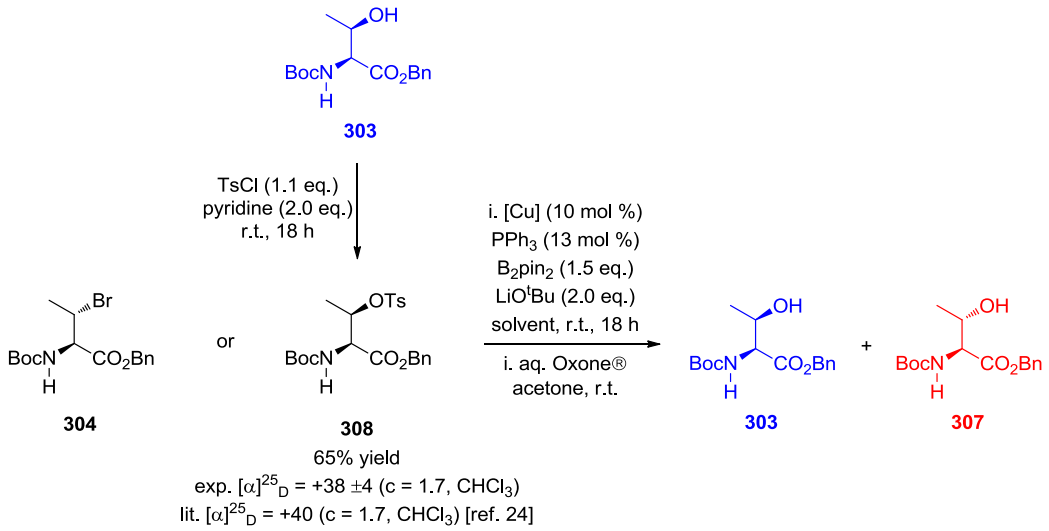


Figure 17. ^{1}H NMR spectrum of a 2:1 mixture of diasteroemeric pairs of diprotected threonines.

With a reliable analytical method in hand, **304** was subjected to the same borylation/oxidation sequence employed on 1-phenylethylbromides (**292**) earlier (***Table 27***, entry 1). From this the diastereochemically pure alcohol (**303**), with the opposite configuration was obtained indicating that the borylation step must proceed with inversion of configuration. An immediate repeat of this reaction afforded the same result (***Table 27***, entry 2). To explore the scope of this steroselectivity, the corresponding enantiomerically pure tosylate (**308**) was prepared from N-Boc-L-threonine benzyl ester (**303**). Optical rotation measurement of the tosylate product was consistent with the reported value from the literature.[24] The subsequent borylation of this under halide-free conditions, however, afforded an unequal mixture of alcohol products **303** and **307** (***Table 27***, entry 3). Switching from THF to the same solvent used for the bromo derivative, DMF, afforded the same mixture of products, ruling out any solvent effects (***Table 27***, entry 4). An identical result was also obtained with a different copper salt, CuOTf.benzene (***Table 27***, entry 5). The original experiment was repeated using freshly prepared **304**, in both THF and DMF solvents, resulting in 1:1 mixtures of **303** and **307** (***Table 27***, entries 6 and 7). The reason for the failure to reproduce the results in entries 1 and 2 is not understood. It should be noted that these reactions (***Table 27***, entries 3 to 7) were carried out several months after the initial reactions outlined in entries 1 and 2. Consequently, different batches of base, CuI and solvent were used in these later experiments.



				isolated yield (%)	product ratio
entry	alkyl-X	[Cu]	solvent	**303**+**307**	**303**:**307**
1	**304**	CuI	DMF	45	100 : 0
2[a]	**304**	CuI	DMF	52	100 : 0
3	**308**	$Cu(MeCN)_4OTf$	THF	42	67 : 33
4	**308**	$Cu(MeCN)_4OTf$	DMF	43	67 : 33
5	**308**	CuOTf.benzene	THF	43	67 : 33
6[b]	**304**	CuI	DMF	44	50 : 50
7[c]	**304**	CuI	THF	40	50 : 50

[a] First repeat of entry 1; [b] second repeat of entry 1; [c] repeat of entry 1 with THF as solvent.

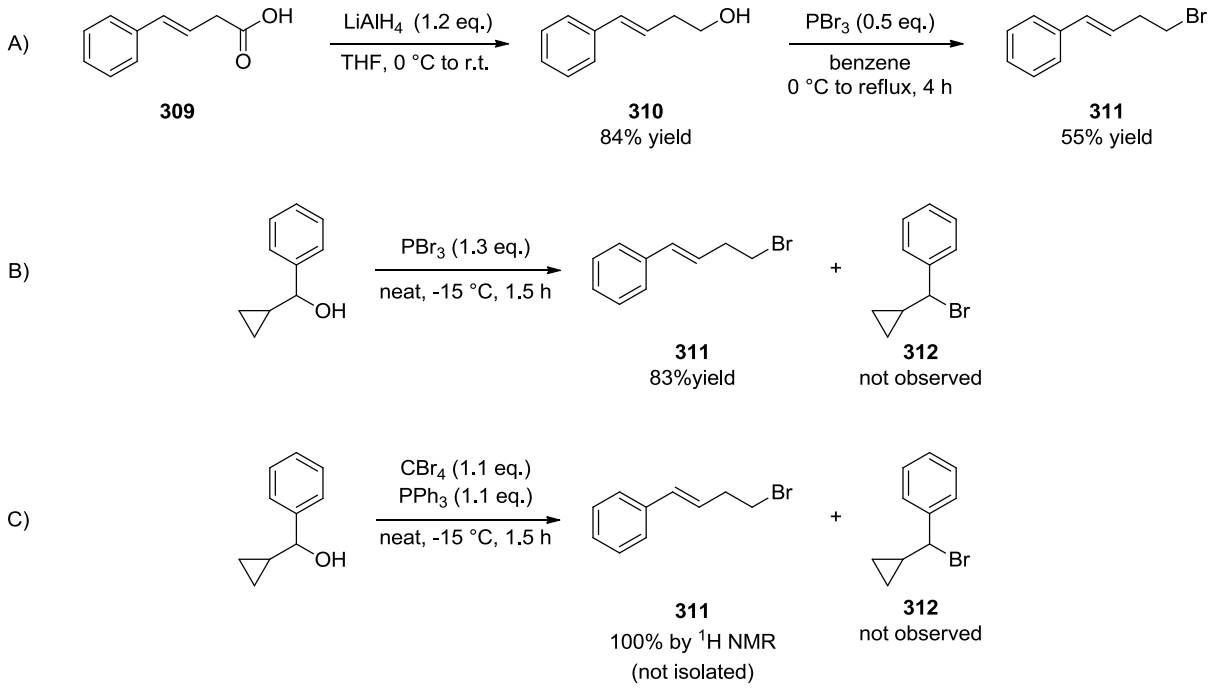
Table 27. Borylation of threonine derivatives

The consistent and reproducible results in the latter series of experiments outlined in ***Table 27*** suggest that the borylation of these substrates actually undergo loss of stereochemistry. Whilst at present the original results cannot be reproduced, it was suspected that these earlier reactions contained an unknown component, which enables the stabilisation of any radical species formed leading to a complete retention of stereochemistry. In order to investigate this further, the borylation of **304** was repeated using PPh_3 and CuI from a variety of sources. However, in all cases, a 1:1 mixture of **303** and **207** was obtained. The

irreproducable results in entries 1 and 2 of ***Table 27*** remain unclear and require further investigation.

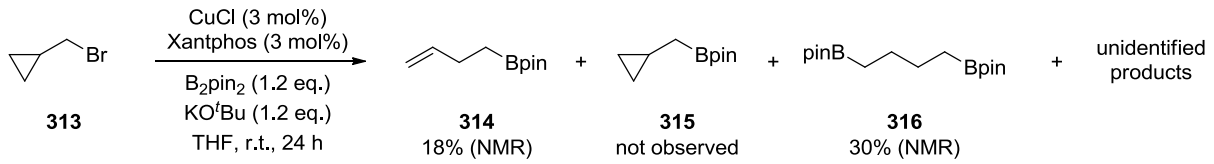
5.3.5 Cyclopropyl Ring-Opening as Evidence for a Radical Mediated Mechanistic Pathway

To further explore the mechanistic pathway of the borylation process, substrates with the propensity for radical-mediated fragmentation were explored. In this regard, cyclopropylmethyl halide derivatives would be expected to ring-open affording a linear product. The work in this area began with attempts to synthesise substrates **311** and **312** as simple and non-volatile variants of the cyclic and linear radical probes (***Scheme 110***). Whilst the synthesis of the bromide compound **311** was easily achieved from $LiAlH_4$ reduction of (E)-4-phenylbut-3-enoic acid (**309**) followed by an Appel reaction (***Scheme 110A***), synthesis of alkyl bromide **312** (***Scheme 110B*** and ***Scheme 110C***) proved problematic as the cyclopropyl motif readily ring-opens to give (bromoethyl)styrene **311**. Such facile ring-opening suggests that compound **312** may not be a suitable radical probe for the borylation reaction.



Scheme 110. Attempts to synthesise cyclopropylmethyl halide derivatives.

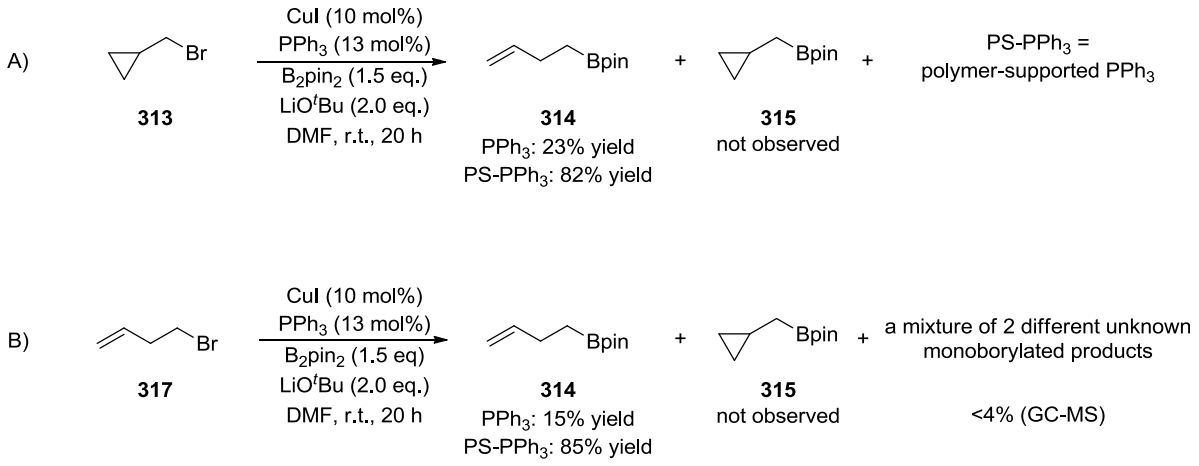
Concurrent with this work, Ito and co-workers reported that borylation of the analogous (bromomethyl)cyclopropane (**313**), under conditions, afforded the linear products **314** and **316** (***Scheme 111***). Whilst the formation of **314** (and absence of **315**) is consistent with a mechanism involving radicals, the formation of bis-borylated product **316** is less obvious.



Scheme 111. Borylation of (bromomethyl)cyclopropane.

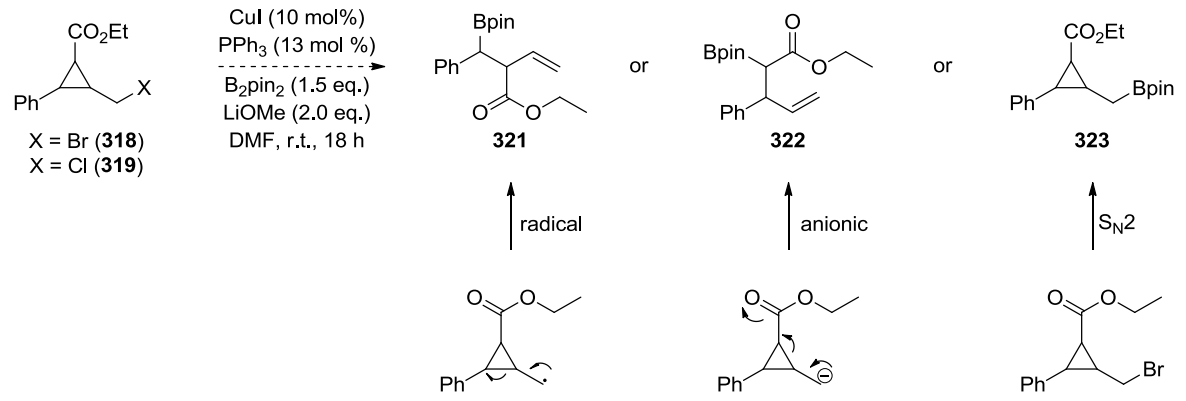
Under the conditions developed reviously in this chapter, however, the borylation of (bromomethyl)cyclopropane proceeded with exclusive formation of linear **314** (the bisborylated product **316** was not observed) (***Scheme 112A***). The low isolated yield of **314**

was due to problematic coelution of PPh_3 during flash column chromatography. An improved isolated yield was achieved when polymer-supported PPh_3 (PS-PPh_3) was employed. Borylation of the linear equivalent of (bromomethyl)cyclopropane in the form of 3-hexenylbromide (**317**) afforded the same product, albeit with a trace amount of two unknown monoborylated products (by GC-MS) (***Scheme 112B***). These results provided a strong argument for a radical mediated pathway hypothesis.



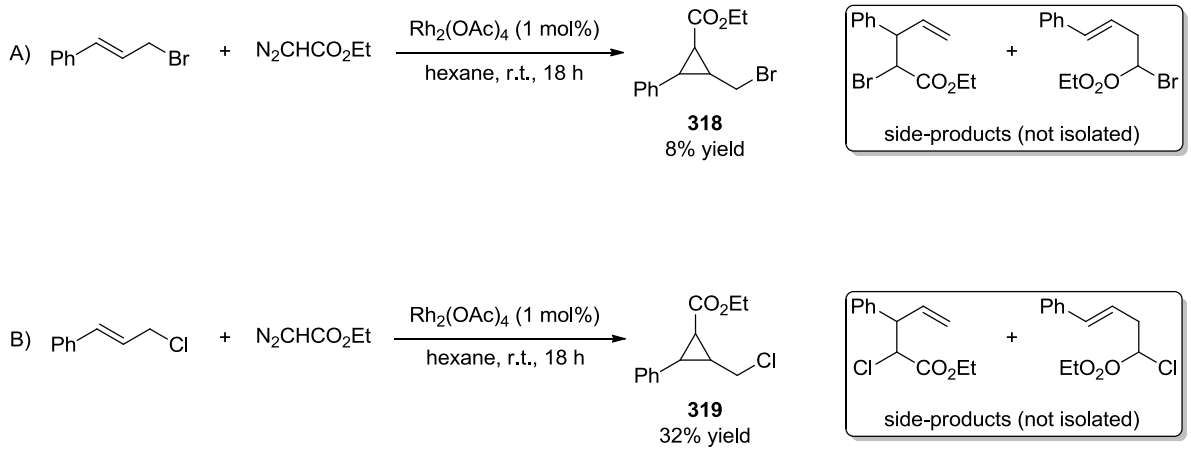
Scheme 112. Borylation of (bromomethyl)cyclopropane and 4-bromo-but-1-ene.

Following these results, it was envisaged that through a suitably sited introduction of an ester group (**318** and **319**), different fragmentation pathways might occur depending on whether an anionic, radical or S_N2 mechanism is involved (***Scheme 113***).



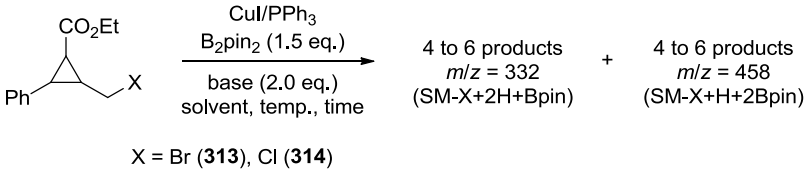
Scheme 113. Hypothesis for differentiating between S_N2, anionic and radical-mediated mechanistic pathways.

In order to test this hypothesis, substrates **318** and **319** were prepared *via* rhodium-catalysed cyclopropanation of cinnamylhalide with ethyldiazoacetate (***Scheme 114A*** and ***Scheme 114B***). The reaction was accompanied by significant amount of Wittig rearrangement but sufficient target compounds could be obtained.

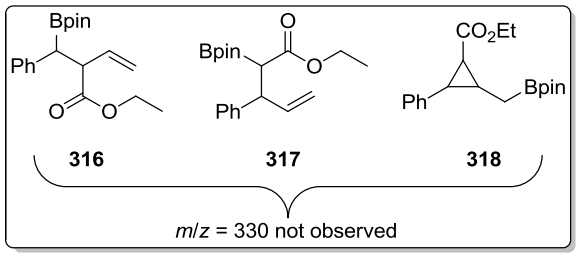


Scheme 114. Synthesis of non-volatile cyclopropyl mechanistic probes.

Disappointingly, borylation of these substrates under a variety of reaction conditions afforded a complex and intractable mixture of products (***Table 28***).



X = Br (**313**), Cl (**314**)



entry	X =	CuI (mol%)	PPh_3 (mol%)	base	solvent	temp.	time (h)
1	Br	10	13	LiOMe	DMF	r.t.	18
2	Cl[a]	10	none	LiO^{t}Bu	THF	60 ˚C	18
3	Cl[b]	10	none	LiO^{t}Bu	THF	60 ˚C	18
4	Cl	10	13	KO^{t}Bu	THF	r.t.	18
5	Cl[c]	10	none	LiO^{t}Bu	THF	r.t.	18
6	Cl[d]	20	none	LiO^{t}Bu	THF	r.t.	72
7	Cl[e]	20	none	LiO^{t}Bu	THF	r.t.	72

[a]reactions performed on both small (0.5 mmol) and large (2.0 mmol) scales; [b]1.0 eq. of TBAI was added; [c]poorer conversion; [d]oxidation of crude reaction mixture with Oxone® afforded 11% recovered starting material; [e]flash column chromatography afforded four separate unidentified set of products; [f]GC-MS trace of these mixtures were less complex than in previous entries.

Table 28. Attempts to borylate non-volatile cyclopropyl derivatives.

It is worth noting, however, that a large number of products with *m*/*z* = 458 were detected by GC-MS in these reactions. This indicates the same addition of an H atom and two Bpin groups observed in Ito's borylation of (bromomethyl)cyclopropane to give bis-borylated compound **316** (***Scheme 111***). Such process could also account for the addition of two H atoms and a Bpin group to give the remaining set of products with *m*/*z* = 332.

5.4 Summary

In conclusion, an unprecedented Cu-catalyzed cross-coupling reaction of unactivated alkyl halides and *pseudo*-halides with diboron reagents have been developed. This reaction can be used to prepare both primary and secondary alkylboronate esters with diverse structures and functional groups, many of which would be difficult to access by other means. The reaction is efficient, practically simple and gives easy isolation of the products that can be further enhanced through the use of polymer-supported ligands. Some evidence of radical mediated pathway was obtained, particularly in the formation of cyclopentylmethylBpin in the borylation of 5-bromohex-1-ene and the loss of stereochemistry from stereochemically pure substrates. However, other mechanistic pathways should not be ruled out as these borylation reactions proceed smoothly in presence of radical scavengers. Further work is required to obtain a better understanding of the full mechanistic pathway of this transformation.

5.5 References

[1] Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525.

[2] Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

[3] Cardenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384.

[4] Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

[5] Hall, D. *Boronic acids : volume 1 : preparation and applications in organic synthesis, medicine and materials*; Wiley-VCH: Weinheim, 2011;

[6] Hall, D. G. *Boronic acids : preparation and applications in organic synthesis and medicine*; Wiley-VCH Verlag GmbH: Weinheim, 2005;

[7] Lillo, V.; Geier, M. J.; Westcott, S. A.; Fernandez, E. *Org. Biomol. Chem.* **2009**, *7*, 4674.

[8] Yang, C. T.; Zhang, Z. Q.; Tajuddin, H.; Wu, C. C.; Liang, J.; Liu, J. H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528.

[9] Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890.

[10] Joshi-Pangu, A.; Ma, X. H.; Diane, M.; Iqbal, S.; Kribs, R. J.; Huang, R.; Wang, C. Y.; Biscoe, M. R. *J. Org. Chem.* **2012**, *77*, 6629.

[11] Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693.

[12] Kleeberg, C.; Dang, L.; Lin, Z. Y.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350.

[13] Yang, C. T.; Zhang, Z. Q.; Liu, Y. C.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3904.

[14] Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086.

[15] Brown, H. C. *Organic syntheses via boranes*; Wiley: New York, 1975;

[16] Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

[17] Giroux, A. *Tetrahedron Lett.* **2003**, *44*, 233.

[18] Burns, D. H.; Miller, J. D.; Chan, H. K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125.

[19] Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969.

[20] Sai, M.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1194.

[21] Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47.

[22] Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982.

[23] Mosher, C. W.; Goodman, L. *J. Org. Chem.* **1972**, *37*, 2928.

[24] Zhou, H.; van der Donk, W. A. *Org. Lett.* **2002**, *4*, 1335.

Chapter 6 - Experimental Details

6.1 General Experimental Considerations

Handling Techniques

Unless otherwise noted, all reactions and air and/or moisture sensitive compounds were carefully prepared and handled in a nitrogen or argon-purged environment, either by Schlenk techniques or in an Innovative Technology Inc. System 1 double-length glovebox.

Solvents

Methyl-*tert*-butyl-ether (MTBE) was bought anhydrous from Sigma Aldrich and was degassed before use. All other reaction solvents were dried using an Innovative Technology Solvent Purification System (SPS) and stored under argon, unless otherwise stated. Petrol refers to distilled light petroleum with boiling point in the 40-60 ◦C range. Ether refers to diethyl ether. Deuterated chloroform ($CDCl_3$), was purchased from Apollo Scientific and were dried over 4 Å molecular sieves and used without further treatment.

Reagents

Bis(pinacolato)diboron was received as a generous donation from Allychem Co. Ltd. (P. R. China) and was used without purification. Unless otherwise stated, all other reagents were purchased from Alfa-Aesar, Acros, Sigma Aldrich or Lancaster, and were used as received.

Microwave Reactor

Individually performed microwave reactions were carried out in septum-containing, crimp-capped, sealed vials in a monomodal Emrys™ Optimizer reactor from Personal Chemistry. The wattage was automatically adjusted to maintain the desired temperature for the desired period of time.

Array Techniques

Injection of solvents and liquid reagents were carried out in air using multi-channel pipettes. Reactions were carried out in 3.0 mL pressure vials fitted with lip-type seal and screwcap. Heating was achieved using an Anton Paar Synthos 3000™ microwave oven (50 Hz) with automatic wattage adjustment to maintain the desired temperature for the stated time. The extraction-separation phase of reaction work-ups was achieved using Biotage Isolute® phase separators with hydrophobic frits. The removal of solvent was carried out under centrifugal force on a Biotage V-10 Evaporator™. Flash column chromatography was carried out on prepacked silica columns (Biotage Isolute® Flash Si II) using automated Flashmaster II purification system using the stated solvent system.

Thin Layer Chromatography

Thin layer chromatography (TLC) were performed on 'Polygram® Sil G/UV' plastic-backed silica plates with 0.2 mm silica gel layer doped with fluorescent indicator.

Dry Loading

Silica gel was added to a solution of the crude product in a volatile organic solvent such as DCM and ether. The mixture was concentrated under reduced pressure to dryness and used in the subsequent silica gel flash column chromatography.

Flash Column Chromatography

Flash column chromatography refers to purification either by manual operation on silica gel (40-63μ mesh size) with the stated solvent system or automated operation using a Teledyne Isco CombiFlash Rf machine on prepacked silica RediSep® Rf cartridge with the stated solvent gradient and at constant flow rate of 35 mL/min.

NMR Spectroscopy

^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) at room-temperature on Varian Mercury-200 (^{1}H), Varian Mercury-400 (^{1}H, ^{13}C, ^{19}F), Bruker Avance-400 (^{1}H, ^{13}C, ^{11}B) , Varian Inova-500 (^{1}H, ^{13}C) or Varian VNMRS-700 (^{1}H, ^{13}C) spectrometers and reported as follows: chemical shift δ (ppm) (multiplicity, coupling constant *J* (Hz), number of protons, assignment). All ^{13}C NMR spectra were proton decoupled. The ^{1}H and ^{13}C chemical shifts are reported using the residual signal of $CHCl_3$ as the internal reference (δH = 7.26 ppm; δC = 77.16 ppm). All chemical shifts are quoted in parts per million relative to tetramethylsilane (δH = 0.00 ppm). ^{11}B NMR spectra are externally calibrated with reference to $BF_3.Et_2O$ (δB = 0.0 ppm). All coupling constants are $^{3}J_{HH}$ unless otherwise stated. Multiplicities are reported using the following abbreviations; s (singlet), d (doublet), t

(triplet), q (quartet), m (unresolved multiplet) and br (broad). Assignment of spectra was carried out using COSY, HSQC, HMBC and NOESY experiments.

Mass Spectrometry

GC-MS analyses were performed using an Agilen 6890N gas chromatograph (column: HP-5MS, 10 m, Ø 0.25 mm, film 0.25 µm; injector: 250 °C; oven: 70 °C (2 min), 70 °C to 250 °C (20 °C min^{-1}), 250 °C (5 min); carrier gas: He (1.6 mL min^{-1})) equipped with an Agilent 5973 inert mass selective detector operating in EI mode and a custom-built Anatune liquid handling system functioning as autosampler/injector. Electrospray (ES) mass spectra were obtained on a Micromass LCT Mass Spectrometer. High-resolution mass spectra were obtained using a Thermo Finnigan LTQFT mass spectrometer or Xevo QToF mass spectrometer (Waters UK, Ltd) by Durham University Mass Spectrometry service.

IR Spectroscopy

Infrared spectra were measured on a Perkin-Elmer Paragon 1000 FT-IR spectrometer *via* the use of a Diamond ATR (attenuated total reflection) accessory (Golden Gate). Assigned peaks are reported in wavenumber (cm^{-1}).

Melting Point

Melting points were recorded using an Electrothermal 9100 capillary melting point apparatus.

6.2 General Procedures

General Procedure A: C-H Borylation of Quinolines (Room Temperature Reaction)

Under N_2, a thick walled microwave synthesis vial was charged with the corresponding arene (1.0 mmol) followed by the addition of 2.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (2.0 mmol). The vessel was sealed with a crimp top septum cap and the reaction mixture was stirred for the time stated at room temperature on a magnetic stirring block. Upon completion, the volatiles were removed under reduced pressure to afford the crude product. This was dry-loaded on to silica gel and purified by silica gel flash column chromatography using the stated conditions for the purified product.

General Procedure B: C-H Borylation of Quinolines (Microwave Heating Conditions)

Under N_2, a thick walled microwave synthesis vial was charged with the corresponding arene (1.0 mmol) followed by the addition of 2.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (2.0 mmol). The vessel was sealed with a crimp top septum cap and the reaction mixture was heated at 100 °C for 1.5 hours in a microwave reactor. Upon completion, the reaction was cooled to room temperature and volatiles were removed under reduced pressure to afford the crude product. This was dry-loaded on to silica gel and purified by silica gel flash column chromatography using the stated conditions for the purified product.

General Procedure C: C-H Borylation of Monosubstituted and Unsymmetrical 1,2-Disubstituted Benzenes with 1,1,2,2-Tetrachloroethane as Internal Standard

Under N_2, a thick walled microwave synthesis vial was charged with the corresponding arene (0.4 mmol) followed by the addition of 1.0 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (0.48 mmol). The vessel was sealed with a crimp top septum cap and the reaction mixture was stirred at room temperature on a magnetic stirring block. After the stated time, the mixture was quenched/diluted with DCM and the volatiles removed under reduced pressure to afford the crude mixture. GC-MS analysis of a small sample, was carried out to determine the % conversion. ^{1}H NMR spectroscopy was carried out on the crude sample to determine the product ratios (to some of these crude were added 1,1,2,2-tetrachloroethane as an internal standard). Structures of the products were confirmed by HCOSY, NOESY, HSQC and HMBC spectroscopic experiments.

General Procedure D: C-H Borylation in an NMR Tube Fitted with a Young's Tap

Under N_2, an NMR tube containing a coaxial tube filled with acetone-d_6 was charged with the corresponding arene (0.2 mmol) followed by the addition of 0.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (0.24 mmol). The NMR tube was sealed with a Young's tap and the homogeneous solution was allowed to stand at room temperature. After the stated time, ^{1}H NMR spectroscopy was carried out on the sample to determine the isomer ratio. GC-MS analysis of a small sample, quenched/diluted with DCM, was carried out to determine the % conversion. Structures of

the products were confirmed by HCOSY, NOESY, HSQC and HMBC spectroscopic experiments.

General Procedure E: "One-Pot" C-H Borylation/Copper-Assisted Suzuki-Miyaura Cross-Coupling Sequence

Under N_2, 5.0 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (2.0 mmol) was transferred to a microwave vial followed by the addition of arene (2.0 mmol). The reaction mixture was heated in a microwave reactor with stirring at 80 °C for the time stated and concentrated under reduced pressure. Under N_2, the mixture was charged with a mixture of $Pd(dppf)Cl_2$ (10 mol%), Cs_2CO_3 (4.0 mmol), aryl halide (2.2 mmol) and CuCl (2.0 mmol) in DMF (6.4 mL). The reaction mixture was heated with stirring at 100 °C for the time stated. The mixture was diluted with water, extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude mixture. Purification by silica gel flash column chromatography was carried out using the stated conditions for the purified product.

General Procedure F: "One-Pot" C-H Borylation/Suzuki-Miyaura Cross-Coupling Sequence

Under N_2, a thick walled microwave synthesis vial was charged with the corresponding arene (1.0 mmol) followed by the addition of 2.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (1.0 mmol). The vessel was sealed with a crimp top septum cap and the reaction mixture was heated at 80 °C for time stated in a microwave reactor. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and analysed by ^1H NMR in $CDCl_3$. To the crude mixture under N_2,

was added a Pd(dppf)Cl_2 (10 mol%), Cs_2CO_3 (0.65 g, 2.0 mmol), CuI (0.19 g, 1.0 mmol) and aryl halide (1.1 mmol) in DMF (8.0 mL). The reaction mixture was heated with stirring at 100 ◦C for the time stated, cooled to room temperature, diluted with water and extracted into ether. The organic phase was dried ovder $MgSO_4$, filtered and concentrated to give a crude mixture. Purification by silica gel flash column chromatography was carried out using the stated conditions for the purified product.

General Procedure G: Preparation of Methyl 2-Substituted Nicotinates and Methyl 2-Substituted Isonicotinates

To a round-bottom flask containing the 2-substituted nicotinic acid or 2-substituted isonicotinic acid (5.0 mmol) was added MeOH (50 mL) and conc. H_2SO_4 (1.0 mL). The mixture was stirred under reflux for 16 h, allowed to cool to room temperature, concentrated under reduced pressure, diluted with water and extracted with ether. The organic was washed with 5% bicarbonate solution until no longer acidic and washed with another portion of water. The organic was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude mixture. This was dry-loaded on to silica gel and purified by silica gel flash column chromatography using the stated conditions for the purified product.

General Procedure H: "One-Pot" Tandem C-H Borylation/1,4-Conjugate Addition Sequence Under Non-Reducing/Schlenk Conditions

Under N_2, a thick walled microwave synthesis vial was charged with the corresponding arene (1.0 mmol) followed by the addition of 2.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (1.0 mmol). The vessel was sealed with

a crimp top septum cap and the reaction mixture was heated at 80 °C for the time stated. Under N_2, the reaction mixture was quenched with aq. KOH (3.8 M, 2.0 mmol, 0.5 ml) and once the resulting effervescence stopped, a solution of $[Rh(cod)Cl]_2$ (5 mg, 1 mol%) in MTBE (2.5 ml) was added followed by the corresponding enone (1.0 mmol). The mixture was heated in a microwave reactor with stirring at 100 °C for the time stated. The mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude mixture. Purification by silica gel flash column chromatography was carried out using the stated conditions for the purified product.

General Procedure I: "One-Pot" Tandem C-H Borylation/1,4-Conjugate Addition Sequence Under Non-Reducing/Array Conditions

In air, a thick walled 3.0 mL microwave vial was charged with the corresponding arene (0.4 mmol) followed by the addition of 2.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (0.4 mmol). The reaction mixture was heated in a microwave reactor with stirring at 100 °C for the time stated. In air, the mixture was quenched with aq. KOH (3.8 M, 0.8 mmol, 0.2 ml) and once the resulting effervescence stopped, a solution of $[Rh(cod)Cl]_2$ (2 mg, 1 mol%) in MTBE (1.0 ml) was added followed by the corresponding enone (0.4 mmol). The mixture was heated in a microwave reactor with stirring at 100 °C for the time stated. The mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude mixture. Purification by silica gel flash column chromatography was carried out using the stated conditions for the purified product.

General Procedure J: "One-Pot" Tandem C-H Borylation/1,4-Conjugate Addition Sequence Under Reducing/Schlenk Conditions

Under N_2, a thick walled microwave synthesis vial was charged with the corresponding arene (1.0 mmol) followed by the addition of 2.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (1.0 mmol). The vessel was sealed with a crimp top septum cap and the reaction mixture was heated at 80 °C for the time stated. Under N_2, the reaction mixture was quenched with aq. KOH (3.8 M, 2.0 mmol, 0.5 ml) and once the resulting effervescence stopped, a solution of $[Rh(cod)Cl]_2$ (5 mg, 1 mol%) in IPA (2.5 ml) was added followed by the corresponding enone (1.0 mmol). The mixture was heated in a microwave reactor with stirring at 100 °C for the time stated. The mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude mixture. Purification by silica gel flash column chromatography was carried out using the stated conditions for the purified product.

General Procedure K: "One-Pot" Tandem C-H Borylation/1,4-Conjugate Addition Sequence Under Reducing/Array Conditions

In air, a thick walled 3.0 mL microwave vial was charged with the corresponding arene (0.4 mmol) followed by the addition of 2.5 mL of an MTBE catalyst stock solution containing $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%) and B_2pin_2 (0.4 mmol). The reaction mixture was heated in a microwave reactor with stirring at 100 °C for the time stated. In air, the mixture was quenched with aq. KOH (3.8 M, 0.8 mmol, 0.2 ml) and once the resulting effervescence stopped, a solution of $[Rh(cod)Cl]_2$ (2 mg, 1 mol%) in IPA (1.0 ml) was added followed by the corresponding enone (0.4 mmol). The mixture was heated in a microwave reactor with

stirring at 100 °C for the time stated. The mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude mixture. Purification by silica gel flash column chromatography was carried out using the stated conditions for the purified product.

General Procedure L: Copper-Catalysed Borylation of Alkyl Bromides

In air, CuI (19 mg, 0.10 mmol), PPh_3 (34 mg, 0.13 mmol), LiOMe (76 mg, 2.0 mmol), and B_2pin_2 (381 mg, 1.5 mmol) were added to a thick walled microwave vial and sealed with a crimp top septum cap. The vessel was evacuated and filled with nitrogen (three cycles). To this was added DMF (2.0 mL) and alkyl bromide (1.0 mmol). The resulting reaction mixture was stirred vigorously at 25 ˚C for 18 h. The reaction mixture was then diluted with EtOAc, filtered through silica gel with copious washings (Et_2O or EtOAc), concentrated, and purified by silica gel flash column chromatography using the stated conditions for the purified product.

General Procedure M: Copper-Catalysed Borylation of Alkyl Iodides

In air, CuI (19 mg, 0.10 mmol), LiO^tBu (160 mg, 2.0 mmol), and B_2pin_2 (381 mg, 1.5 mmol) were added to a thick walled microwave vial and sealed with a crimp top septum cap. The vessel was evacuated and filled with nitrogen (three cycles). To this was added THF (2.0 mL) and alkyl iodide (1.0 mmol). The resulting reaction mixture was stirred vigorously at 25 ˚C for 18 h. The reaction mixture was then diluted with EtOAc, filtered through silica gel with copious washings (Et_2O or EtOAc), concentrated, and purified by silica gel flash column chromatography using the stated conditions for the purified product.

General Procedure N: Copper-Catalysed Borylation of Alkyl Chlorides

In air, CuI (19 mg, 0.10 mmol), LiO^tBu (160 mg, 2.0 mmol), NBu_4I (368 mg, 1.0 mmol), and B_2pin_2 (381 mg, 1.5 mmol) were added to a thick walled microwave vial and sealed with a crimp top septum cap. The vessel was evacuated and filled with nitrogen (three cycles). To this was added THF (2.0 mL) and alkyl chloride (1.0 mmol). The resulting reaction mixture was stirred vigorously at 60 ˚C for 18 h. The reaction mixture was then diluted with EtOAc, filtered through silica gel with copious washings (Et_2O or EtOAc), concentrated, and purified by silica gel flash column chromatography using the stated conditions for the purified product.

General Procedure O: Copper-Catalysed Borylation of Alkyl Tosylates

In air, CuI (19 mg, 0.10 mmol), LiO^tBu (160 mg, 2.0 mmol), NBu_4I (368 mg, 1.0 mmol), and B_2pin_2 (381 mg, 1.5 mmol) were added to a thick walled microwave vial and sealed with a crimp top septum cap. The vessel was evacuated and filled with nitrogen (three cycles). To this was added MeCN (2.0 mL) and alkyl tosylate (1.0 mmol). The resulting reaction mixture was stirred vigorously at 60 ˚C for 18 h. The reaction mixture was then diluted with EtOAc, filtered through silica gel with copious washings (Et_2O or EtOAc), concentrated, and purified by silica gel flash column chromatography using the stated conditions for the purified product.

General Procedure P: Tosylation of Alcohols

In air, pyridine (1.58 g, 20.0 mmol) was added over 4 hours to an ice-cooled solution of the alcohol (10.0 mmol) and toluenesulfonyl chloride (2.10 g, 11.0 mmol). The reaction mixture

was acidified with aq. HCl (1.0 M), extracted with ether, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by silica gel flash column chromatography was carried out using the stated conditions for the purified product.

General Procedure for the Preparation of a Catalyst Stock Solution for C-H Borylation

Under N_2, a catalyst stock solution was prepared by weighing $[Ir(cod)OMe]_2$ (100 mg, 0.15 mmol), dtbpy (80 mg, 0.30 mmol) and B_2pin_2 (2.54 g, 10.0 mmol) into a volumetric flask followed by the addition of MTBE to make up 25 ml of solution. The flask was vigorously shaken and left to sit at room temperature until the solution developed a deep red color and no more solid was visible (~ 1 h). The solution was transferred to and stored in a crimp-cap, septum-sealed tube and used within 3 days.

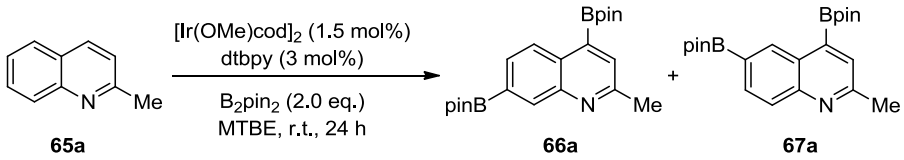
General Procedure for the Preparation of a Catalyst Stock Solution for 1,4-Conjugate Addition

Under N_2, a catalyst stock solution was prepared by weighing $[Rh(cod)Cl]_2$ (20 mg, 0.04 mmol) into a volumetric flask followed by the addition of stated solvent to make up 10 ml of solution. The flask was vigorously shaken and briefly heated with a heat gun to ensure that all solid had dissolved. The solution was transferred to and stored in a crimp-cap, septum-sealed tube and used within 12 h.

6.4 Experimental details

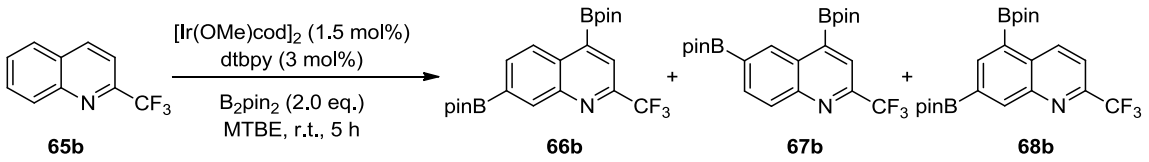
Borylation of Quinolines

Borylation of 2-methyquinoline (65a)



General procedure A was applied to 2-methylquinoline (**65a**) on a smaller scale (57 mg, 0.40 mmol). The reaction mixture was stirred for 24 hours giving a conversion of >95% and a mixture of monoborylated products (minor) and bisborylated products (major) (GC-MS). Analysis of ^{1}H NMR spectrum showed **66a** and **67a** in a 68:32 mixture, some unreacted starting material (**65a**), and small amounts of an unknown product.

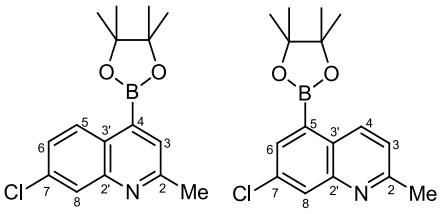
Borylation of 2-(trifluoromethyl)quinoline (65b)



General procedure A was applied to 2-(trifluoromethyl)quinoline (**65b**) (79 mg, 0.40 mmol). The reaction mixture was stirred for 5 hours giving a conversion of 90% (GC-MS) and **66b**, **67b** and **68b** in a 51:42:7 mixture (^{1}H NMR spectrum).

7-Chloro-2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)quinoline (63f)

7-Chloro-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)quinoline (64f)



63f **64f**

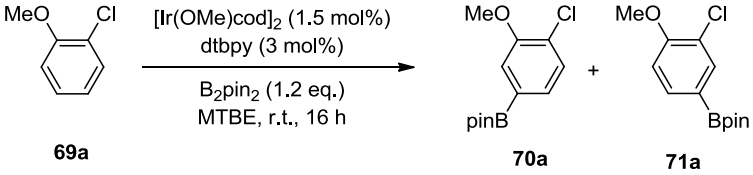
General procedure B was applied to 7-chloro-2-methylquinoline (**62f**) (177 mg, 1.0 mmol). The reaction afforded a 65:35 mixture of 2 monoborylated products at 92% conversion, as determined by GC-MS. Purification by silica gel flash-column chromatography (0-12.5%, MeOH/DCM, 25 column volumes) afforded a mixture of 7-chloro-2-methylquinoline (**62f**) and 7-chloro-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)quinoline as yellow oil. Recrystallisation from minimum amount of MeCN afforded 7-chloro-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)quinoline (**64f**) as a white crystalline solid (33 mg, 11%); m.p. 149 - 150 °C (from MeCN); ν_{max} ($CHCl_3$) 3020, 1475, 1362, 1226, 1016, 928, 793 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.6, 1H, 4-C***H***), 8.09 (d, *J* = 2.2, 1H, 6-C***H***), 8.00 (d, *J* = 2.2, 1H, 8-C***H***), 7.30 (d, *J* = 8.6, 1H, 3-C***H***), 2.72 (s, 3H, 2-C***H***$_3$), 1.41 (s, 12H, pin-C***H***$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.9 (***C***-2), 148.6 (***C***-2'), 136.9 (***C***-4), 135.7 (***C***-8), 134.8 (***C***-7), 131.1 (***C***-6), 128.8 (***C***-3'), 122.6 (***C***-3), 84.5 (pin-***C***$(CH_3)_2$), 25.5 (2-***C***H_3), 25.2 (pin-***C***H_3); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.64; GC-MS (EI) *m/z* 305 ($[M]^+$, ^{37}Cl), 303 ($[M]^+$, ^{35}Cl), 290 ($[M\text{-}CH_3]^+$, ^{37}Cl), 288 ($[M\text{-}CH_3]^+$, ^{35}Cl), 247 ($[M\text{-}CO(CH_3)_2]^+$, ^{37}Cl), 245 ($M\text{-}CO(CH_3)_2]^+$, ^{35}Cl), 221 ($[M\text{-}C(CH_3)_2C(CH_3)_2]^+$, ^{37}Cl), 219 ($[M\text{-}C(CH_3)_2C(CH_3)_2]^+$, ^{35}Cl), 205 ($[M\text{-}CO(CH_3)_2C(CH_3)_2]^+$, ^{37}Cl), 203 ($[M\text{-}CO(CH_3)_2C(CH_3)_2]^+$, ^{35}Cl); HRMS (ASAP) *m/z* calculated $[M+H]^+$ 304.1276, found $[M+H]^+$ 304.1282.

Further elution afforded 7-chloro-2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)quinoline (**63f**) as white crystalline solid (185 mg, 61%), ν_{max} ($CHCl_3$) 2981, 1589, 1493, 1371, 1329, 1262, 1183, 1138, 964, 933, 928, 843 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.4, 1H, 5-C***H***), 8.00 (d, *J* = 2.1, 1H, 8-C***H***), 7.74 (s, 1H, 3-C***H***), 7.44 (dd, *J* = 2.1, 8.4, 1H, 6-C***H***), 2.73 (s, 3H, 2-C$\boldsymbol{H_3}$), 1.42 (s, 12H, pin-C$\boldsymbol{H_3}$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.3 (***C***-2), 148.3 (***C***-2'), 134.9 (***C***-7), 130.0 (***C***-3), 129.6 (***C***-5), 128.1 (***C***-8), 127.7 (***C***-3'), 126.9 (***C***-6), 84.8 (pin-***C***$(CH_3)_2$), 25.3 (2-***C***H_3), 25.1 (pin-***C***H_3); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.90; GC-MS (EI) *m/z* 305 ($[M]^+$, ^{37}Cl), 303 ($[M]^+$, ^{35}Cl), 290 ($[M\text{-}CH_3]^+$, ^{37}Cl), 288 ($[M\text{-}CH_3]^+$, ^{35}Cl), 245 ($[M\text{-}(CH_3)_2CO]^+$, ^{35}Cl), 219 ($[M\text{-}C(CH_3)_2C(CH_3)_2]^+$, ^{37}Cl), 217 ($[M\text{-}C(CH_3)_2C(CH_3)_2]^+$, ^{35}Cl), 205 ($[M\text{-}CO(CH_3)_2C(CH_3)_2]^+$, ^{37}Cl), 203 ($[M\text{-}CO(CH_3)_2C(CH_3)_2]^+$, ^{35}Cl); HRMS (ASAP) *m/z* calculated $[M+H]^+$ 304.1276, found $[M+H]^+$ 304.1281.

Application of general procedure A with 7-chloro-2-methylquinoline (**62f**) (177 mg. 1.00 mmol) for 68 h afforded 73:27 mixture of **63f**:**64f** at 93% conversion, as determined by ^1H NMR spectrum analysis of the crude mixture. Purification of the crude mixture, as above, afforded 7-chloro-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)quinoline (**64f**) as a white crystalline solid (30 mg, 10%) and 7-chloro-2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)quinoline (**63f**) as white crystalline solid (200 mg, 66%).

Borylation of Unsymmetrical 1,2-Disubstituted Benzenes

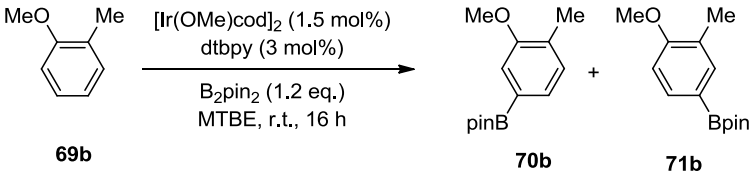
Borylation of 1-chloro-2-methoxybenzene (69a)



69a **70a** **71a**

General procedure C was applied to 1-chloro-2-methoxybenzene (**69a**) (57 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 94% (GC-MS) and **70a** and **71a** in a 60:40 mixture which also contained unreacted starting material (**69a**) (^{1}H NMR spectrum).

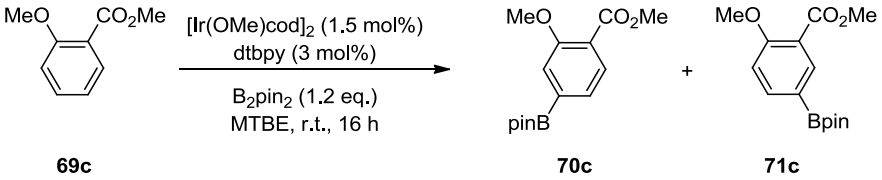
Borylation of 1-methoxy-2-methylbenzene (69b)



69b **70b** **71b**

General procedure C was applied to 1-methoxy-2-methylbenzene (**69b**) (50 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 75% (GC-MS) and **70b** and **71b** in a 75:25 mixture which also contained unreacted starting material (**69b**) (^{1}H NMR spectrum).

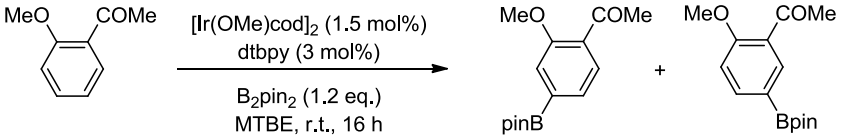
Borylation of methyl 2-methoxybenzoate (69c)



69c **70c** **71c**

General procedure C was applied to methyl 2-methoxybenzoate (**69c**) (66 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS) and **70c** and **71c** in a 85:15 mixture (^{1}H NMR spectrum).

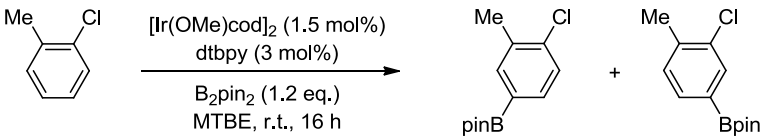
Borylation of 1-(2-methoxyphenyl)ethanone (69d)



69d **70d** **71d**

General procedure C was applied to 1-(2-methoxyphenyl)ethanone (**69d**) (60 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS) and **70d** and **71d** in a 89:11 mixture (^{1}H NMR spectrum) and some unreacted starting material (**69d**).

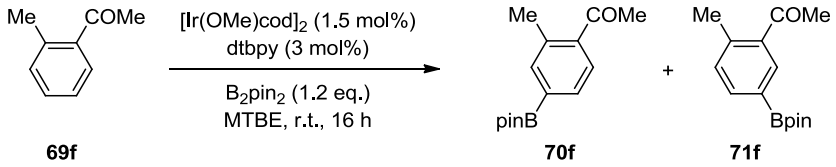
Borylation of 1-chloro-2-methylbenzene (69e)



69e **70e** **71e**

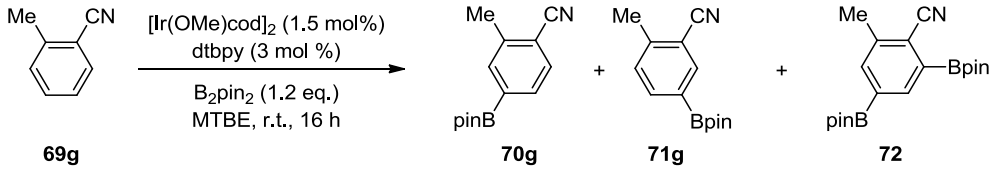
General procedure C was applied to 1-chloro-2-methylbenzene (**69e**) (51 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 h giving a conversion of >99% (GC-MS) and **70e** and **71e** in a 34:66 mixture (^{1}H NMR spectrum).

Borylation of 1-(2-methylphenyl)ethanone (69f)



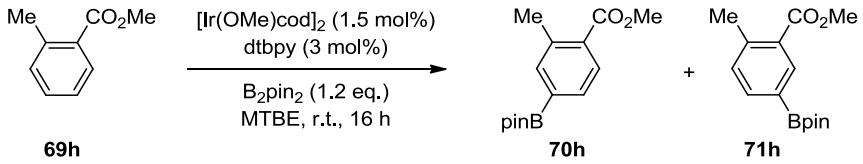
General procedure C was applied to 1-(2'-methylphenyl)ethanone (**69f**) (54 mg, 0.4 mmol). The reaction mixture was was stirred at room temperature for 16 hours giving a conversion of 87% (GC-MS) and **70f** and **71f** in a 56:44 mixture which also contained unreacted starting material (**69f**) (^{1}H NMR spectrum).

Borylation of 2-methylbenzonitrile (69g)



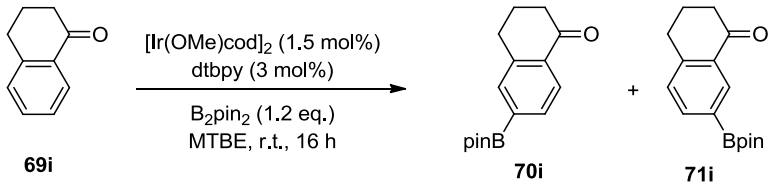
General procedure C was applied to 2-methylbenzonitrile (**69g**) (47mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS) and **70g**, **71g** and **72** in a 52:40:8 mixture (^{1}H NMR spectrum).

Borylation of methyl 2-Methylbenzoate (69h)



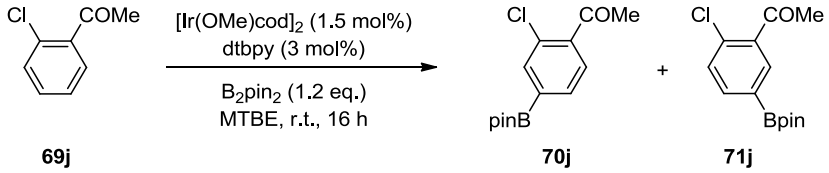
General procedure D was applied to methyl 2-methylbenzoate (**69h**) (30 mg, 0.2 mmol). The reaction mixture was allowed to stand for 16 hours giving a conversion of >99% (GC-MS) and **70h** and **71h** in a 73:27 mixture (^{1}H NMR spectrum).

Borylation of 3,4-dihydronaphthalen-1(2*H*)-one (69i)



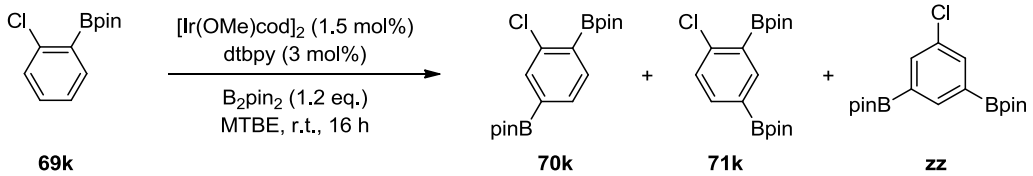
General procedure D was applied to 3,4-dihydronaphthalen-1(2*H*)-one (**69i**) (29 mg, 0.2 mmol). The reaction mixture was allowed to stand for 16 hours giving a conversion of >99% (GC-MS) and **70i** and **71i** in a 80:20 mixture (^{1}H NMR spectrum).

Borylation of 1-(2-chlorophenyl)ethanone (69j)



General procedure C was applied to 1-(2-chlorophenyl)ethanone (**69j**) (57 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS) and **70j** and **71j** in a 62:38 mixture (^{1}H NMR spectrum).

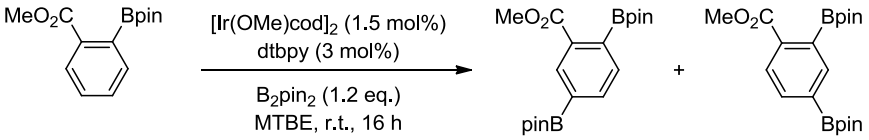
Borylation of 2-(2-Chlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (69k)



General procedure C was applied to 2-(2-chlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**69k**) (96 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS) and monoborylated products

(**70k**+**zz** arising from trace chlorobenzene impurity in the reaction mixture) and **71k** in a 84:16 mixture (^{1}H NMR spectrum).

Borylation of methyl 2-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)benzoate (69l)

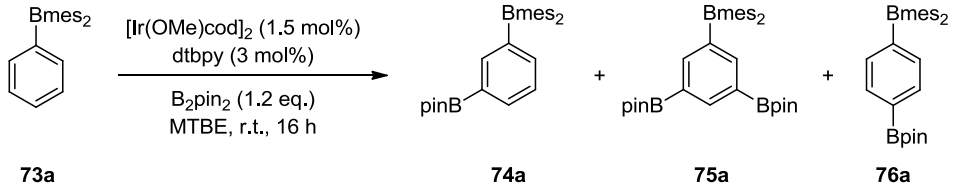


69l **70l** **71l**

General procedure D was applied to 2-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)benzoate **69l** (52 mg, 0.2 mmol). The reaction mixture was allowed to stand for 16 hours giving a conversion of 35% (GC-MS) and **70l** and **71l** in a 53:47 mixture (GC-MS). These peaks were assigned based on the trend of other 1,2-disubstituted benzenes as the structures of both **70l** and **71l** could not be determined unambiguously by NMR spectroscopic techniques.

Borylation of Monosubstituted Benzenes

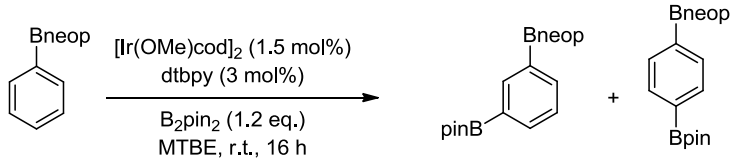
Borylation of (dimesitylboryl)benzene (73a)



73a **74a** **75a** **76a**

General procedure C was applied to (dimesitylboryl)benzene (**73a**) (132 mg, 0.40 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 69% (^{1}H NMR spectrum) and **74a**, **75a** and **76a** in a 26:6:68 mixture and some unreacted starting material (**19a**) (^{1}H NMR spectrum).

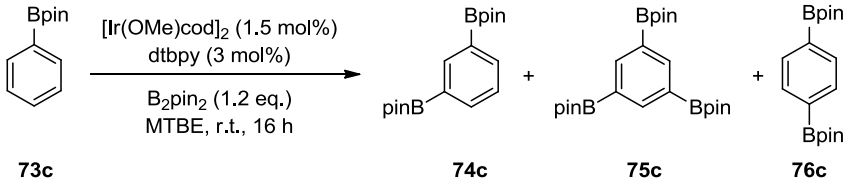
Borylation of 5,5-dimethyl-2-phenyl-[1,3,2]-dioxaborinane (73b)



73b **74b** **76b**

General procedure C was applied to 5,5-dimethyl-2-phenyl-[1,3,2]-dioxaborinane (**73b**) (76 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 45% (^{1}H NMR spectrum) and **74b** and **76b** in a 33:67 mixture and some unreacted starting material (**19b**) (^{1}H NMR spectrum).

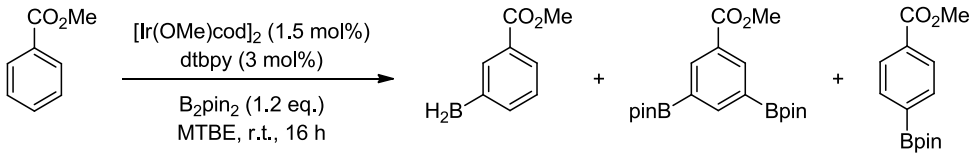
Borylation of 4,4,5,5-tetramethyl-2-phenyl-[1,3,2]-dioxaborolane (73c)



73c **74c** **75c** **76c**

General procedure C was applied to 4,4,5,5-tetramethyl-2-phenyl-[1,3,2]-dioxaborolane (**73c**) (82 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 71% (^{1}H NMR spectrum) and **74c, 75c** and **76c** in a 32:4:64 mixture and some unreacted starting material (**73c**) (^{1}H NMR spectrum).

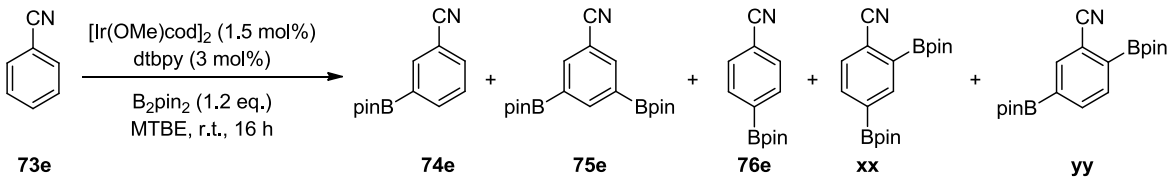
Borylation of methyl benzoate (73d)



73d **74d** **75d** **76d**

General procedure C was applied to methyl benzoate (**73f**) (54 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS) and **74d**, **75d** and **76d** in a 22:22:56 mixture (^{1}H NMR spectrum).

Borylation of benzonitrile (73e)

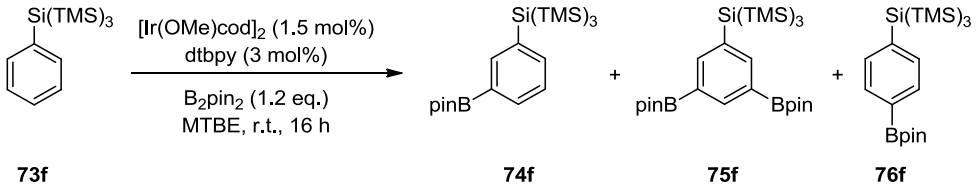


73e **74e** **75e** **76e** **xx** **yy**

General procedure C was applied to benzonitrile (**73e**) (41 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS)

and **74e**, **75e**, **76e**, **xx** and **yy** in a 30:21:34:7:8 mixture and some unreacted starting material (**73e**) (^{1}H NMR spectrum).

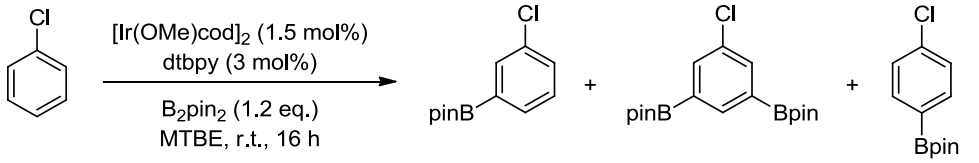
Borylation of 1,1,1,3,3,3-hexamethyl-2-phenyl-2-(trimethylsilyl)trisilane (73f)



73f **74f** **75f** **76f**

General procedure C was applied to 1,1,1,3,3,3-hexamethyl-2-phenyl-2-(trimethylsilyl)trisilane (**73f)** (130 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 72% (GC-MS) and **74f**, **75f** and **76f** in a 48:15:37 mixture and some unreacted starting material (**73f**) (^{1}H NMR spectrum).

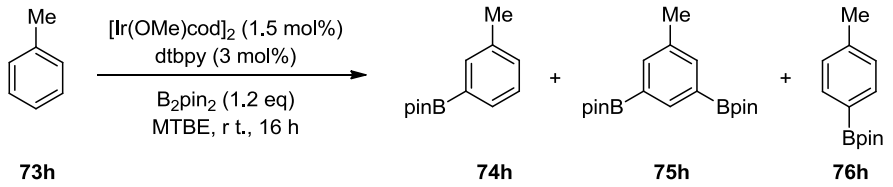
Borylation of chlorobenzene (73g)



73g **74g** **75g** **76g**

General procedure C was applied to chlorobenzene (**73g**) (45 mg, 0.4 mmol). The reaction mixture was allowed to stand for 16 h giving a conversion of 98% (GC-MS) and **74g**, **75g** and **76g** in a 32:33:35 mixture (^{1}H NMR spectrum).

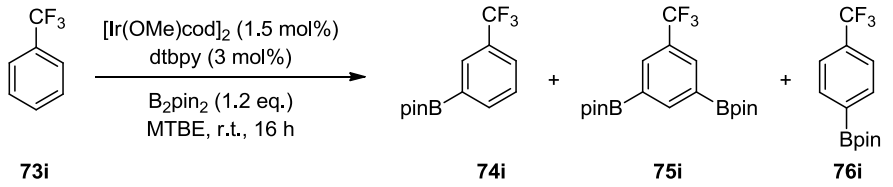
Borylation of toluene (73h)



73h **74h** **75h** **76h**

General procedure D was applied to toluene (**73h**) (19 mg, 0.2 mmol). The reaction mixture was allowed to stand for 16 hours giving a conversion of 30% (GC-MS) and **74h**, **75h** and **76h** in a 63:6:31 mixture and some unreacted starting material (**19h**) (^{1}H NMR spectrum).

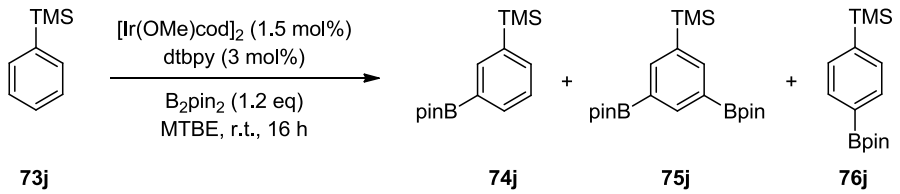
Borylation of (trifluoromethyl)benzene (73i)



73i **74i** **75i** **76i**

General procedure C was applied to (trifluoromethyl)benzene (**73i**) (58 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of >99% (GC-MS) and **74i**, **75i** and **76i** in a 29:40:31 mixture (^{1}H NMR spectrum).

Borylation of trimethyl(phenyl)silane (73j)

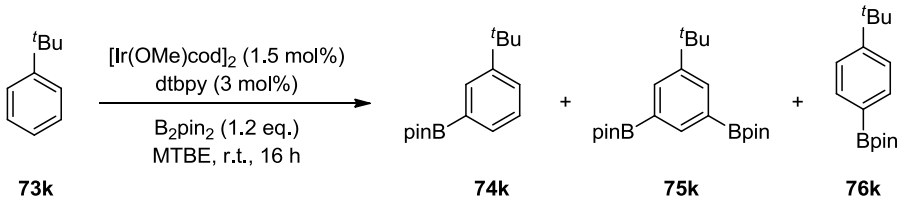


73j **74j** **75j** **76j**

General procedure C was applied to trimethyl(phenyl)silane (**73j**) (60 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 93%

(GC-MS) and **74j**, **75j** and **76j** in a 56:16:28 mixture and some unreacted starting material (**73j)** (^{1}H NMR spectrum).

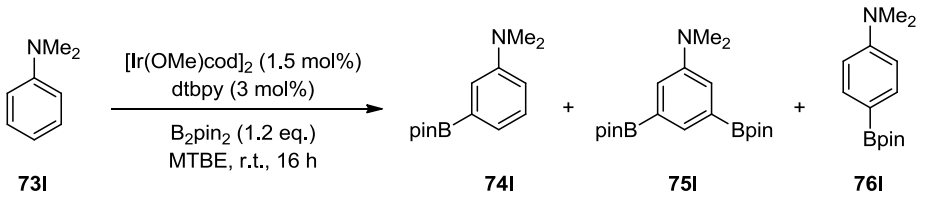
Borylation of *tert*-butylbenzene (73k)



73k **74k** **75k** **76k**

General procedure C was applied to *tert*-butylbenzene (**73k**) (54 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 82% (GC-MS) and **74k**, **75k** and **76k** in a 68:8:24 mixture and some unreacted starting material (**73k**) (^{1}H NMR spectrum).

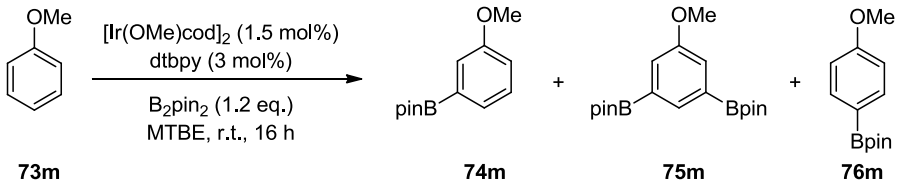
Borylation of *N*,*N*-dimethylaniline (73l)



73l **74l** **75l** **76l**

General procedure C was applied to *N*,*N*-dimethylaniline (**73l**) (48 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 69% (GC-MS) and **74l**, **75l** and **76l** in a 75:4:21 mixture and some unreacted starting material (**73l**) (^{1}H NMR spectrum).

Borylation of anisole (73m)

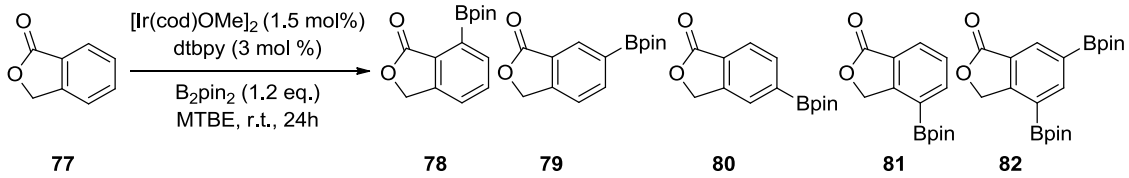


73m **74m** **75m** **76m**

General procedure C was applied to anisole (**73m**) (43 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 16 hours giving a conversion of 93% (GC-MS) and **74m**, **75m** and **76m** in a 68:16:16 mixture and some unreacted starting material (**73m**) (^{1}H NMR spectrum).

Phthalide Experiments

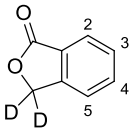
Borylation of phthalide (77)



77 78 79 80 81 82

General procedure D was applied to phthalide **77** (27 mg, 0.2 mmol). The reaction mixture was allowed to stand for 24 hours giving a conversion of >99% (GC-MS) and borylated products (**78, 79, 80, 81** and **82**) in a 6:6:28:31:29 mixture (^{1}H NMR spectrum).

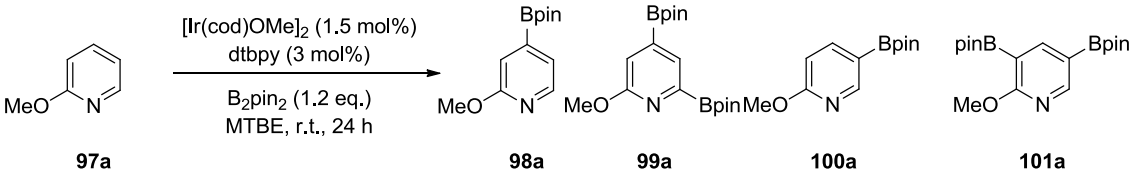
Phthalide-d_2 (86)[1]



Procedures taken from Bailey[2] and Vitullo.[3] A solution of phthalic anhydride (**85**) (1.78 g, 12.0 mmol) in DMF (16 mL) was added slowly to an ice-cooled suspension of $NaBD_4$ (0.42 g, 10.0 mmol) in DMF (4.0 mL). The mixture was allowed to warm to room temperature, concentrated under reduced pressure, diluted with water, extracted into ether, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (40g column, 0-100% ether/hexane, 16 column volumes) afforded phthalide-d_2 (**86**) as a white solid (1.4 g, 86%); m.p. 73 - 74 °C; ν_{max} (neat) 1742, 1463, 1262, 1120, 1008, 938, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6, 1H, 2-***H***), 7.68 (t, *J* = 7.6, 1H, 4-***H***), 7.49-7.55 (m, 2H, 3,5-***H***), ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (***C***=O), 146.5 (***C***-6), 134.1 (***C***-4), 129.2 (***C***-3), 125.9 (***C***-1,2), 122.3 (***C***-5), 69.17 (***C***D_2); GC-MS (EI) *m/z* 136 $[M]^+$, 106 $[M\text{-}CD_2O]^+$, 78 $[M\text{-}CO_2CD_2]^+$

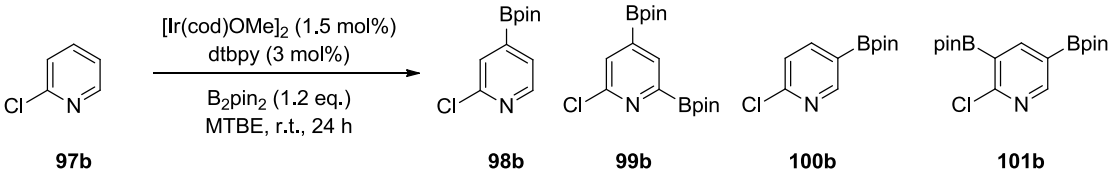
Borylation of 2-Substituted Pyridines

Borylation of 2-methoxy pyridine (97a)



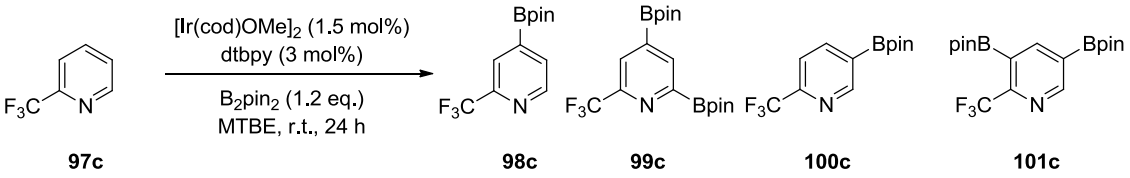
General procedure D was applied to 2-methoxypyridine (**97a**) (22 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h giving a conversion of >99% (GC-MS) and **98a**, **99a**, **100a** and **101a** in a 30:9:45:16 mixture (^{1}H NMR spectrum).

Borylation of 2-methoxy pyridine (97b)



General procedure D was applied to 2-chloropyridine (**97b**) (23 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h giving a conversion of >99% (GC-MS) and **98b**, **99b**, **100b** and **101a** in a 30:9:45:16 mixture (^{1}H NMR spectrum).

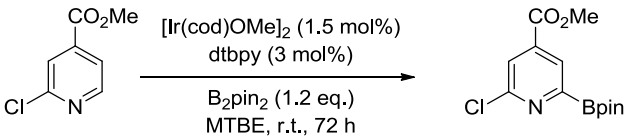
Borylation of 2-methoxy pyridine (97c)



General procedure D was applied to 2-methoxypyridine (**97c**) (30 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h giving a conversion of >99% (GC-MS) and **98c**, **99c**, **100c** and **101c** in a 30:9:45:16 mixture (^{1}H NMR spectrum).

Borylation of 2,4-Disubstituted Pyridines

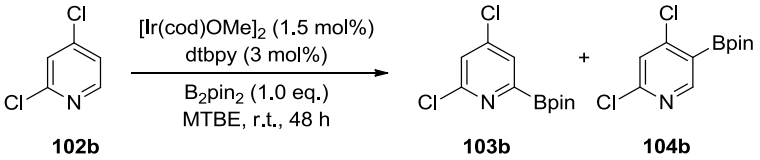
Borylation of methyl 2-chloroisonicotinate (102a)



102a **103a**

General procedure D was applied to methyl 2-chloroisonicotinate (**102a**) (34 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 72 h giving a conversion of >73% to 6-borylated product (**103a**) (^{1}H NMR spectrum).

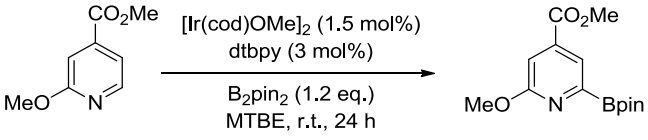
Borylation of 2,4-dichloropyridine (102b)



102b **103b** **104b**

General procedure D was applied to 2,4-dichloropyridine (**102b**) (30 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 48 h giving a conversion of >73% and **103b** and **104b** in a 55:45 mixture (^{1}H NMR spectrum).

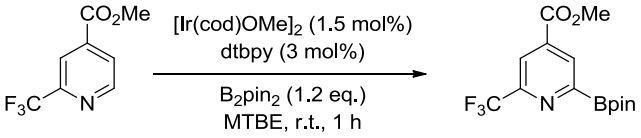
Borylation of methyl 2-methoxyisonicotinate (102c)



102c **103c**

General procedure D was applied to methyl 2-methoxyisonicotinate (**102c**) (33 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h giving a conversion of 57% to 6-borylated product (**103c**) (^{1}H NMR spectrum).

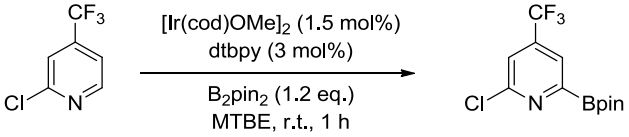
Borylation of methyl 2-(trifluoromethyl)isonicotinate (102d)



102d **103d**

General procedure D was applied to methyl 2-(trifluoromethyl)isonicotinate (**102d**) (41 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 h giving a conversion of 93% to 6-borylated product (**103d**) (^{1}H NMR spectrum).

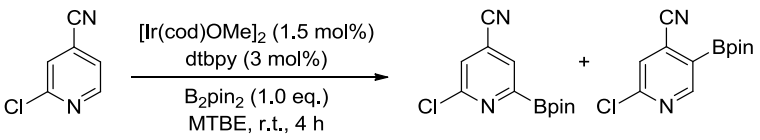
Borylation of 2-chloro-4-(trifluoromethyl)pyridine (102e)



102e **103e**

General procedure D was applied to 2-chloro-4-(trifluoromethyl)pyridine (**102d**) (36 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 h giving a conversion of 61% to 6-borylated product (**103e**) (^{1}H NMR spectrum).

Borylation of 2-chloroisonicotinonitrile (102f)



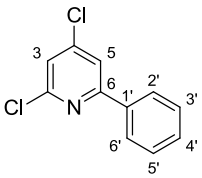
102f **103f** **104f**

General procedure D was applied to 2-chloroisonicotinonitrile (**102f**) (28 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 4 h giving a conversion of 42% and **103b** and **104b** in a 57:43 mixture (^{1}H NMR spectrum).

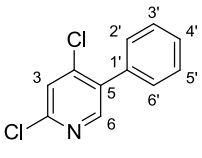
"One-Pot" C-H Borylation/Suzuki-Miyaura Cross-Coupling Sequence

2,4-Dichloro-6-phenylpyridine (109b)

2,4-Dichloro-5-phenylpyridine (110b)



109b



110b

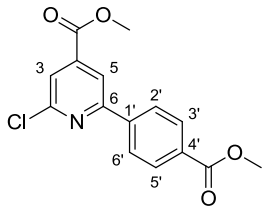
General procedure E was applied to 2,4-dichloropyridine (**102b**) (296 mg, 2.0 mmol) with 4-iodobenzene (449 mg, 2.2 mmol). ^{1}H NMR analysis after C-H borylation showed 95% conversion with 55:45 mixture 6- and 5-borylated products. Purification by flash column chromatography (24 g column, 0-10% EtOAc/hexane, 25 column volumes) afforded 2,4-dichloro-6-phenylpyridine (**109b**) (179 mg, 40%) and 2,4-dichloro-5-phenylpyridine (**110b**) (125 mg, 28%), both as colourless liquid.

109b: ν_{max} (neat) 3058, 2928, 1742, 1568, 1542, 1408, 1369, 1157, 1068, 844, 800, 796, cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.98 (m, 2H, 2',6'-C***H***), 7.66 (d, ^{4}J = 1.4, 1H, 5-C***H***), 7.46-7.50 (m, 3H, 3',4',5'-C***H***, 7.30 (d, J = 1.4, 1H, 3-C***H***); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.1 (***C***-6), 152.1 (***C***-1'), 146.4 (***C***-4), 136.8 (***C***-2), 130.4 (***C***-4'), 129.1 (***C***-3',5'), 127.2 (***C***-2',6'), 122.4 (***C***-3), 119.4 (***C***-5); GC-MS (EI) *m/z* 227 ([M]$^{+}$, ^{37}Cl^{37}Cl), 225 ([M]$^{+}$, ^{37}Cl^{35}Cl), 223 ([M]$^{+}$, ^{35}Cl^{35}Cl), 190 ([M-Cl]$^{+}$, ^{37}Cl), 188 ([M-Cl]$^{+}$, ^{35}Cl), 153 [M-2Cl]$^{+}$; HRMS (ASAP) calculated [M]$^{+}$ 222.9950, found [M]$^{+}$ 222.9953.

119b: ν_{max} (neat) 3058, 2928, 1742, 1568, 1542, 1408, 1369, 1157, 1068, 844, 800, 796, cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.34 (s, 1H, 6-***H***), 7.49-7.46 (m, 4H), 7.42 (d, J = 2.0, 2H); ^{13}C NMR

(176 MHz, $CDCl_3$) δ 150.8 (***C***-6), 150.7, 144.3, 135.6, 134.4, 129.6, 128.7, 124.9; GC-MS (EI) *m/z* 227 ($[M]^+$, $^{37}Cl^{37}Cl$), 225 ($[M]^+$, $^{37}Cl^{35}Cl$), 223 ($[M]^+$, $^{35}Cl^{35}Cl$), 190 $[M-Cl]^+$, ^{37}Cl), 188 ([M-Cl]+, ^{35}Cl), 153 $[M-2Cl]^+$; HRMS (ASAP) calculated $[M]^+$ 222.9950, found $[M]^+$ 222.9955.

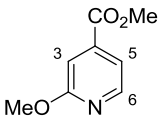
Methyl 2-chloro-6-(4-(methoxycarbonyl)phenyl)isonicotinate (106)



General procedure E was applied to methyl 2-chloroisonicotinate (**102a**) (172 mg, 1.0 mmol) with methyl 4-iodobenzoate (288 mg, 1.1 mmol). ^1H NMR analysis after C-H borylation showed 78% conversion to the 6-borylated product. Purification by flash column chromatography (40 g column, 0-40% ether/hexane, 20 column volumes) afforded methyl 2-chloro-6-(4-(methoxycarbonyl)phenyl)isonicotinate (**106**) as a white solid (70 mg, 53%); m.p. 167 - 168 °C; ν_{max} (neat) 1720, 1551, 1402, 1315, 1266, 1108, 968, 763 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.25 (d, *J* = 1.4, 1H, 5-C***H***), 8.15-8.12 (m, 4H, 2',3',5',6'-C***H***), 7.85 (d, *J* = 1.4, 1H, 3-C***H***), 4.00 (s, 3H, Py-$CO_2C\boldsymbol{H}_3$), 3.95 (s, 3H, Ph-$CO_2C\boldsymbol{H}_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.7 (4'-C***C***O_2), 164.5 (4-C***C***O_2), 157.8 (***C***-6), 152.5 (***C***-4), 141.2 (***C***-2), 141.0 (***C***-1'), 131.6 (***C***-4'), 130.3 (***C***-3',5'), 127.2 (***C***-2',6'), 123.0 (***C***-3), 118.7 (***C***-5), 53.3 (4-$CCO_2\boldsymbol{C}H_3$), 52.4 (4'-$CCO_2\boldsymbol{C}H_3$); GC-MS (EI) *m/z* 307 ($[M]^+$, ^{37}Cl), 305 ($[M]^+$, ^{35}Cl), 276 ($[M-OCH_3]^+$, ^{37}Cl), 274 ($[M-OCH_3]^+$, ^{35}Cl), 248 ($[M-CO_2CH_3]^+$, ^{37}Cl), 246 ($[M-CO_2CH_3]^+$, ^{35}Cl), 189 ($[M-(CO_2CH_3)_2]^+$, ^{37}Cl), 187 ($[M-(CO_2CH_3)_2]^+$, ^{35}Cl), 152 $[M-(CO_2CH_3)_2Cl]^+$; HRMS (ASAP) calculated $[M]^+$ 305.0449, found $[M]^+$ 305.0451.

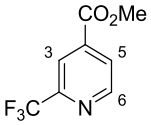
Preparation of Methyl 2-Substituted Nicotinates and Isonicotinates

Methyl 2-methoxyisonicotinate (102c)[4]



General procedure G was applied to 2-methoxyisonicotinic acid (0.84 g, 5.0 mmol) Purification by flash column chromatography (12 g column, 0-50% ether/hexane, 28 column volumes) afforded methyl 2-methoxyisonicotinate (**102c**) as colourless liquid (0.51 g, 65%); ν_{max} (neat) 2952, 1732, 1564, 1454, 1386, 1324, 1262, 1219, 1097, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.4, 1H, 3-C***H***), 7.39 (dd, *J* = 5.4, 1H, 5-C***H***), 7.30 (m, 1H, 6-C***H***), 3.96 (s, 3H, OC***H***$_3$), 3.93 (s, 3H, O_2C***H***$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7 (***C***=O), 150.0 (***C***-2), 147.8 (***C***-3), 140.2 (***C***-4), 115.8 (***C***-5), 111.4 (***C***-6), 54.0 (O***C***H_3), 52.8 (O_2***C***H_3); GC-MS (EI) *m/z* 167 $[M]^+$, 166 $[M-H]^+$, 136 $[M-OCH_3]^+$, 122 $[M-O_2Me]^+$, 108 $[M-CO_2Me]^+$, 95 $[M-CO_2Me-CH_3]^+$; HRMS (ASAP) calculated $[M]^+$ 167.1647, found $[M]^+$ 167.1651.

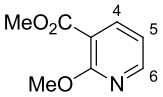
Methyl 2-(trifluoromethyl)isonicotinate (102d)[5]



General procedure G was applied to 2-(trifluoromethyl)isonicotinic acid (1.03 g, 5.0 mmol). Purification by silica flash column chromatography (12g column, 0-50% ether/hexane, 28 column volumes) afforded methyl 2-methoxyisonicotinate (**102d**) as colourless liquid (0.30 g, 58%); ν_{max} (neat) 2962, 1737, 1333, 1260, 1186, 1143, 765, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 4.8, 1H, 6-C***H***), 8.23 (m, 1H, 3-C***H***), 8.06 (d, *J* = 4.8, 1H, 5-C***H***), 4.00 (s, 3H,

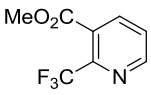
C***H***$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.4 (***C***-2), 151.1 (***C***=O), 149.5 (q, $^2J_{C\text{-}F}$ = 35, ***C***CF_3), 139.2 (***C***-4), 125.9 (***C***-5), 121.3 (q, $^1J_{C\text{-}F}$ = 275, ***C***F_3), 120.051 (***C***-3), 53.292 (***C***H_3); GC-MS (EI) *m/z* 205 $[M]^+$, 186 $[M\text{-}F]^+$, 174 $[M\text{-}OCH_3]^+$, 146 $[M\text{-}CO_2CH_3]^+$; HRMS (ASAP) calculated $[M]^+$ 205.0345, found $[M]^+$ 205.0351.

Methyl 2-methoxynicotinate (116a)[6]



General procedure G was applied to 2-methoxynicotinic acid (0.84 g, 5.0 mmol) Purification by flash column chromatography (12 g column, 0-50% ether/hexane, 28 column volumes) afforded methyl 2-methoxynicotinate (**116a**) as colourless liquid (0.46 g, 58%); ν_{max} (neat) 2952, 1734, 1706, 1676, 1466, 1400, 1316, 1236, 1084, 1010, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 4.8, ^4J = 2.4, 1H, 6-C***H***), 8.15 (dd, *J* = 7.8, ^4J = 1.8, 1H, 4-C***H***), 6.94 (dd, *J* = 4.8 and 7.8, 1H, 5-C***H***), 4.04 (s, 3H, C***H***$_3CO_2$), 3.90 (s, 3H, C***H***$_3$O); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7 (***C***=O), 162.5 (***C***-2), 141.3 (***C***-4), 116.4 (***C***-5), 114.1 (***C***-3), 54.2 (***C***H_3CO_2), 52.4 (O***C***H_3); GC-MS (EI) *m/z* 167 $[M]^+$, 166 $[M\text{-}H]^+$, 136 $[M\text{-}OCH_3]^+$, 122 $[M\text{-}O_2Me]^+$, 108 $[M\text{-}CO_2Me]^+$, 95 $[M\text{-}CO_2Me\text{-}CH_3]^+$; HRMS (ASAP) calculated $[M]^+$ 167.1647, found $[M]^+$ 167.1650.

Methyl 2-(trifluoromethyl)nicotinate (116b)[5]

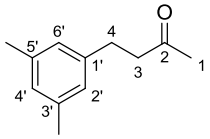


General procedure G was applied to 2-(trifluoromethyl)nicotinic acid (1.03 g, 5.0 mmol). Purification by silica flash column chromatography (12g column, 0-50% ether/hexane, 28

column volumes) afforded methyl 2-methoxynicotinate (**116b**) as colourless liquid (0.32 g, 61%); ν_{max} (neat) 2952, 1734, 1589, 1440, 1306, 1262, 1182, 1138, 1120, 1058, 788, 638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 5.7, 1H, 6-C***H***), 8.11 (d, *J* = 8.7, 1H, 4-C***H***), 7.58 (dd, J = 8.7, 5.7, 1H, 5-C***H***), 3.97 (s, 3H, C***H***$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.0 (***C***=O), 151.0 (***C***-6), 145.8 (q, 2JCF = 35, ***C***-2), 138.4 (***C***-4), 129.9 (***C***-3), 121.2 (***C***F_3), 53.4 (***C***H_3); GC-MS (EI) *m/z* 205 $[M]^+$, 186 $[M-F]^+$, 174 $[M-OCH_3]^+$, 146 $[M-CO_2CH_3]^+$; HRMS (ASAP) calculated $[M]^+$ 205.0345, found $[M]^+$ 205.0349.

"One-Pot" Tandem C-H Borylation/1,4-Conjugate Addition Sequence Under Non-Reducing Conditions

4-(3,5-Dimethylphenyl)butan-2-one (163)[7]

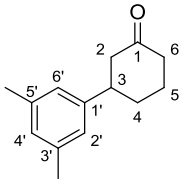


general procedure	reaction times (min) C-H borylation	1,4-conjugate addition	isolated yield (%)
H (Schlenk)	60	30	68
I (array)	60	30	45

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 3014, 2920, 2360, 1716, 1606, 1450, 1362, 1158, 850, 698, 518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H, 4'-C***H***), 6.81 (s, 2H, 2',6'-C***H***), 2.73-2.85 (m, 4H, *3,* 4-C***H***$_2$), 2.29 (s, 6H, 3',5'-CC***H***$_3$), 2.15 (s, 3H, 1-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1 (2-***C***), 140.9 (1'-***C***), 138.0 (3',5'-***C***), 127.7 (4'-***C***), 126.1 (2',6'-***C***), 45.3 (3-***C***), 30.0 (1-***C***), 30.0 (4-***C***), 21.2 (3',5'-C***C***H$_3$); GC-MS (EI) *m/z* 176 $[M]^+$, 161 $[M\text{-}CH_3]^+$, 133 $[M\text{-}CH_3CO]^+$, 105 $[(CH_3)_2C_6H_3]^+$; HRMS (ASAP) calculated $[M]^+$ 176.1201, found $[M]^+$ 176.1191.

3-(3,5-Dimethylphenyl)cyclohexanone (194)[8]



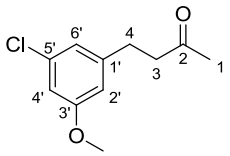
general procedure	reaction times (min) C-H borylation	1,4-conjugate addition	isolated yield (%)
H (Schlenk)	60	30	65
I (array)	60	30	55

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2938, 2868, 1708, 1602, 1222, 848, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H, 4'-C***H***), 6.84 (s, 2H, 2',6'-C***H***), 2.90-2.98 (m, 1H, 3-C***H***), 2.34-2.61 (m, 4H,

2,6-C***H***$_2$), 2.32 (s, 6H, 3',5'-CC***H***$_3$), 2.04-2.19 (m, 2H, 4-C***H***$_2$), 1.74-1.90 (m, 2H, 5-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2 (1-***C***), 144.4 (1'-***C***), 138.2 (3',5'-***C***), 128.3 (4'-***C***), 124.4 (2',6'-***C***), 49.0 (2-***C***), 44.7 (3-***C***), 41.2 (6-***C***), 32.9 (5-***C***), 25.6 (4-***C***), 21.3 (C***C***H_3); GC-MS (EI) *m/z* 202 $[M]^+$, 187 $[M\text{-}CH_3]^+$, 159 $[M\text{-}CH_2CO]^+$, 145 $[M\text{-}CH_2CH_2CO]^+$, 132 $[M\text{-}CH_2CH_2CH_2C{=}O]^+$; HRMS (ASAP) calculated $[M]^+$ 202.1358, found $[M]^+$ 202.1350.

4-(3-Chloro-5-methoxyphenyl)butan-2-one (164)

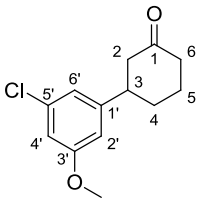


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	20	30	71
I (array)	60	30	69

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2942, 2838, 1714, 1574, 1460, 1430, 1364, 1316, 1264, 1150, 1056, 840, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (m, 1H, 2'-C***H***), 6.74 (m, 1H, 4'-C***H***), 6.63 (m, 1H, 6'-C***H***), 3.79 (s, 3H, OC***H***$_3$), 2.73-2.86 (m, 4H, 3,4-C***H***$_2$), 2.16 (s, 3H, 1-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3 (2-***C***), 160.3 (5'-***C***), 143.9 (1'-***C***), 134.7 (5'-***C***), 120.7 (2'-***C***), 112.9 (4'-***C***), 111.8 (6'-***C***), 55.4 (O***C***H_3), 44.6 (3-***C***), 30.1 (1-***C***), 29.4 (4-***C***), 21.2 (3',5'-C***C***H_3); GC-MS (EI) *m/z* 214 ($[M]^+$, ^{37}Cl), 212 ($[M]^+$, ^{35}Cl), 271 ($[M\text{-}CH_3CO]^+$, ^{37}Cl), 269 ($[M\text{-}CH_3CO]^+$, ^{35}Cl), 157 ($[M\text{-}CH_3(CO)CH_2]^+$, ^{37}Cl), 155 ($[M\text{-}CH_3(CO)CH_2]^+$, ^{35}Cl); HRMS (ASAP) calculated $[M+H]^+$ 213.0682, found $[M+H]^+$ 213.0669.

3-(3-Chloro-5-methoxyphenyl)cyclohexanone (195)

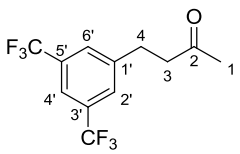


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	20	30	68
I (array)	60	30	63

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2942, 2872, 1708, 1574, 1458, 1430, 1316, 1276, 1222, 1150, 1052, 846, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (m, 1H, 6'-C***H***), 6.77-6.78 (m, 1H, 4'-C***H***), 6.65 (m, 1H, 2'-C***H***), 2.80 (s, 3H, OC***H***$_3$), 2.91-2.99 (m, 1H, 3-C***H***), 2.33-2.61 (m, 4H, 2,6-C***H***$_2$), 2.06-2.19 (m, 2H, 4-C***H***$_2$), 1.71-1.88 (m, 2H, 5-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.3, 160.4 (3'-***C***), 147.1 (1'-***C***), 135.0 (5'-***C***), 119.1 (6'-***C***), 112.1 (2'-***C***), 111.5 (4'-***C***), 55.5 (O***C***H_3), 48.6 (2-***C***), 44.5 (3-***C***), 41.1 (6-***C***), 32.5 (5-***C***), 25.4 (4-***C***); GC-MS (EI) *m/z* 240 ($[M]^+$, ^{37}Cl), 238 ($[M]^+$, ^{35}Cl), 199 ($[M\text{-}CHCO]^+$, ^{37}Cl), 197 ($[M\text{-}CHCO]^+$, ^{35}Cl), 171 ($[M\text{-}(CH_2)_3CO]^+$, ^{37}Cl), 169 ($[M\text{-}(CH_2)_3CO]^+$, ^{35}Cl); HRMS (ASAP) calculated $[M]^+$ 239.0839, found $[M]^+$ 239.0847.

4-(3,5-Bis(trifluoromethyl)phenyl)butan-2-one (166)



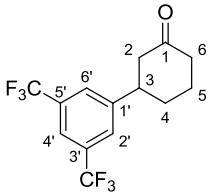
general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	20	30	53
I (array)	60	30	45

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2974, 2934, 1720, 1380, 1276, 1166, 1124, 892, 842, 706, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H, 4'-C***H***), 7.66 (s, 2H, 2',6'-**C*H***), 3.03 (t, 2H, *J* = 8, 4-C***H***$_2$), 2.84 (t, 2H, *J* = 8, 3-C***H***$_2$), 2.19 (s, 3H, 1-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4 (2-***C***), 143.6

(1'-***C***), 131.7 (q, $^{2}J_{C\text{-}F}$ = 33, 3',5'-***C***), 128.7 (m, 2',6'-***C***), 123.34 (q, $^{1}J_{C\text{-}F}$ = 271, ***C***F_3), 120.2 (m, 4'-***C***), 44.2 (3-***C***), 30.0 (1-***C***), 29.1 (4-***C***); ^{19}F NMR (376 MHz, $CDCl_3$) δ 63.32; GC-MS (EI) *m/z* 284 $[M]^+$, 265 $[M\text{-}F]^+$, 241 $[M\text{-}COCH_3]^+$, 227 $[M\text{-}CH_2COCH_3]^+$; HRMS (ASAP) calculated $[M]^+$ 284.0636, found $[M]^+$ 284.0635.

3-(3,5-Bis(trifluoromethyl)phenyl)cyclohexanone (196)

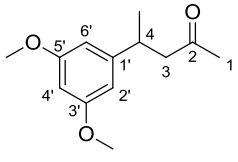


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	20	30	55
I (array)	60	30	47

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2950, 2884, 1716, 1382, 1358, 1274, 1168, 1124, 934, 902, 842, 706, 682 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H, 4'-C***H***), 7.69 (s, 2H, 2',6'-C***H***), 3.12-3.20 (m, 1H, 3-C***H***), 2.38-2.67 (m, 4H, 2,6-C***H***$_2$), 2.13-2.26 (m, 2H, 4-C***H***$_2$), 1.77-1.97 (m, 2H, 5-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (1-***C***), 146.6 (1'-***C***), 132.0 (q, $^{2}J_{C\text{-}F}$ = 33, 3',5'-***C***), 123.3 (q, $^{1}J_{C\text{-}F}$ = 273, ***C***F_3), 126.9 (m, 2',6'-***C***), 120.9 (4'-***C***), 48.4 (2-***C***), 44.4 (3-***C***), 40.9 (6-***C***), 32.4 (5-***C***), 25.3 (4-***C***); ^{19}F NMR (376 MHz, $CDCl_3$) δ 63.30; GC-MS (EI) *m/z* 310 $[M]^+$, 291 $[M\text{-}F]^+$, 267 $[M\text{-}HCOCH_2]^+$, 254 $[M\text{-}(CH_2)_2CO]^+$, 240 $[M\text{-}(CH_2)_3CO]^+$; HRMS (ASAP) calculated $[M+H]^+$ 311.0871, found $[M+H]^+$ 311.0865.

4-(3,5-Dimethoxyphenyl)pentan-2-one (197)

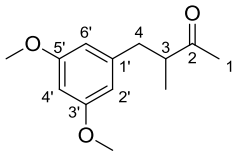


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	20	30	47
I (array)	20	40	36

Flash colum chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2960, 2838, 1712, 1592, 1460, 1428, 1356, 1204, 1150, 1054, 1050, 832, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, 2H, ^{4}J = 4 Hz, 2',6'-C***H***), 6.31 (t, 1H, ^{4}J = 2 Hz, 4'-C***H***), 3.79 (s, 6H, OC***H***$_3$), 3.21-3.30 (m, 1H, 4-C***H***), 2.60-2.78 (m, 2H, 3-C***H***$_2$), 2.09 (s, 3H, 1-C***H***$_3$), 1.25 (d, 3H, *J* = 8, 4-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7 (2-***C***), 160.9 (3',5'-***C***), 148.8 (1'-***C***), 105.0 (2',6'-***C***), 98.0 (4'-***C***), 55.3 (O***C***H_3), 51.9 (3-***C***), 35.7 (4-***C***), 30.6 (1-***C***), 21.9 (4-C***C***H_3); GC-MS (EI) *m/z* 222 $[M]^+$, 179 $[M\text{-}CH_3CO]^+$, 165 $[M\text{-}CH_2COCH_3]^+$; HRMS (ASAP) calculated $[M+H]^+$ 223.1334, found $[M+H]^+$ 233.1321.

4-(3,5-Dimethoxyphenyl)-3-methylbutan-2-one (198)

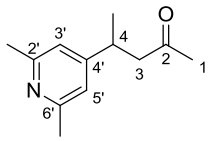


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	20	30	45
I (array)	20	40	30

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2942, 2840, 1710, 1596, 1458, 1428, 1354, 1204, 1158, 1056, 834, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (2, 3H, 2',4',6'-C***H***), 3.78 (s, 6H, OC***H***$_3$), 2.81-2.98 (m, 2H, 4-C***H***$_2$), 2.47-2.53 (m, 1H, 3-C***H***), 2.12 (s, 3H, 1-C***H***$_3$), 1.10-1.11 (d, 3H, *J* = 4, 3-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.1 (2-***C***), 160.8 (3',5'-***C***), 142.1 (1'-***C***), 107.0 (2',6'-***C***), 98.2 (4'-***C***), 55.3 (O***C***H_3), 48.6 (3-***C***), 39.2 (4-***C***), 28.9 (1-***C***), 16.3 (3-C***C***H_3); GC-MS (EI) *m/z* 222 $[M]^+$, 179 $[M\text{-}CH_3CO]^+$, 151 $[M\text{-}CH_3CHCOCH_3]^+$; HRMS (ASAP) calculated $[M+H]^+$ 223.1334, found $[M+H]^+$ 223.1312.

4-(2,6-Dimethylpyridin-4-yl)pentan-2-one (199)[9]

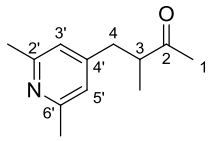


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	5	30	46
I (array)	20	40	35

Flash column chromatography: 0-25% MeOH/DCM

Colourless oil; ν_{max} (neat) 3428, 2968, 2924, 1714, 1606, 1566, 1426, 1362, 1162, 868 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, 3',5'-C***H***), 3.18-3.27 (m, 1H, 4-C***H***), 2.62-2.77 (m, 2H, 3-C***H***$_2$), 2.50 (s, 6H, 2',6'-CC***H***$_3$), 2.10 (s, 3H, 1-C***H***$_3$), 1.23 (d, 3H, *J* = 8, 4-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8 (2-***C***), 157.9 (2',6'-***C***), 155.6 (4'-***C***), 118.7 (3',5'-***C***), 50.9 (3-***C***), 34.5 (4-***C***H), 30.5 (1-***C***H$_3$), 24.5 (2',6'-C***C***H$_3$), 21.3 (4-C***C***H$_3$); LC-MS (ES) *m/z* 192 $[M+H]^+$; HRMS (ES) calculated $[M+H]^+$ 192.1388, found $[M+H]^+$ 192.1384.

4-(2,6-Dimethylpyridin-4-yl)-3-methylbutan-2-one (200)



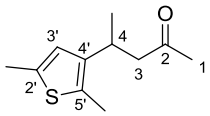
general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	5	30	42
I (array)	20	40	30

Flash column chromatography: 0-25% MeOH/DCM

Colourless oil; ν_{max} (neat) 3400, 2968, 2972, 2932, 1710, 1608, 1566, 1420, 1360, 1164, 854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 2H, 3',5'-C***H***), 2.80-2.96 (m, 2H, 4-C***H***$_2$), 2.49 (s, 6H, 2',6'-CC***H***$_3$), 2.43-2.49 (m, 1H, 3-C***H***), 2.13 (s, 3H, 1-C***H***$_3$), 1.11 (d, 3H, *J* = 8, 3-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2 (2-*C*), 157.7 (2',6'-*C*), 149.3 (4'-*C*), 120.8 (3',5'-***C***), 47.8 (3-***C***), 37.8

(4-***C***), 28.7 (1-***C***H_3), 24.4 (2',6'-C***C***H_3), 16.5 (3-C***C***H_3); LC-MS (ES) *m/z* 192 $[M+H]^+$; HRMS (ASAP) calculated $[M+H]^+$ 192.1388, found $[M+H]^+$ 192.1370.

4-(2,5-Dimethylthiophen-3-yl)pentan-2-one (201)

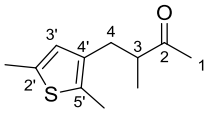


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	5	30	39
I (array)	20	40	30

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2974, 2924, 2873, 1712, 1455, 1355, 1174, 1144, 828, 499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 1H, 3'-C***H***), 3.27-3.36 (m, 1H, 4-C***H***), 2.55-2.68 (m, 2H, 3-C***H***$_2$), 2.39 (s, 3H, 2'-CC***H***$_3$), 2.32 (s, 3H, 5'-CC***H***$_3$), 2.06 (s, 3H, 1-C***H***$_3$), 1.17 (d, 3H, *J* = 8, 4-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (2-***C***), 141.1 (4'-***C***), 135.7 (2'-***C***), 129.9 (5'-***C***), 123.7 (3'-***C***), 51.4 (3-C***H***$_2$), 30.5 (4-***C***H), 28.8 (1-***C***H_3), 21.6 (4-C***C***H_3), 15.2 (2'-C***C***H_3), 12.7 (5'-CC***H***$_3$); GC-MS (EI) *m/z* 196 $[M]^+$, 153 $[M-CH_3CO]^+$, 139 $[M-CH_2COCH_3]^+$; HRMS (ASAP) calculated $[M]^+$ 196.0922, found $[M]^+$ 196.0922.

4-(2,5-Dimethylthiophen-3-yl)-3-methylbutan-2-one (202)



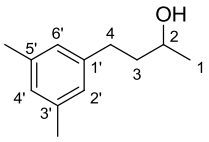
general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
H (Schlenk)	5	30	42
I (array)	20	40	37

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 2972, 2920, 2872, 1712, 1454, 1356, 1174, 1144, 828, 496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H, 3'-C***H***), 2.72-2.81 (m, 2H, 4-C***H***$_2$), 2.40-2.47 (m, 1H, 3-C*H*), 2.38 (s, 3H, 2'-CC***H***$_3$), 2.29 (s, 3H, 5'-CC***H***$_3$), 2.10 (s, 3H, 1-C***H***$_3$), 1.08-1.09 (d, 3H, *J* = 4, 4-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4 (2-***C***), 135.3 (4'-***C***), 134.7 (2'-***C***), 131.4 (5'-***C***), 126.9 (3'-***C***), 48.0 (3-***C***), 31.3 (4-***C***H_2), 28.90 (1-***C***H_3), 16.3 (3-C***C***H_3), 15.1 (2'-C***C***H_3), 12.7 (5'-C***C***H_3); GC-MS (EI) *m*/*z* 196 $[M]^+$, 153 $[M\text{-}CH_3CO]^+$, 125 $[M\text{-}CH_3CHCOCH_3]^+$;HRMS (ES) calculated $[M+H]^+$ 197.1000, found $[M+H]^+$ 197.0997.

"One-Pot" Tandem C-H Borylation/1,4-Conjugate Addition Sequence Under Reducing Conditions

4-(3,5-Dimethylphenyl)butan-2-ol (186)



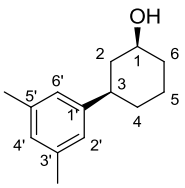
general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	60	80	61
K (array)	60	80	46

Flash column chromatography: 0-50% MTBE/cyclohexane

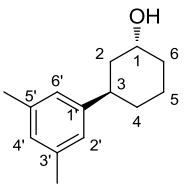
Colourless oil; ν_{max} (neat) 3344, 2964, 2922, 2862, 1606, 1456, 1374, 1128, 1070, 962, 934, 840, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 3H, 2',4',6'-C***H***), 3.81-3.87 (m, 1H, 2-C***H***), 2.57-2.73 (m, 2H, 4-C***H***$_2$), 2.30 (s, 6H, 3',5'-CC***H***$_3$), 1.73-1.79 (m, 2H, 3-C***H***$_2$), 1.33-1.34 (d, 1H, *J* = 4, O***H***), 1.23-1.24 (d, 3H, 1-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (1'-***C***), 137.9 (3',5'-***C***), 127.5 (4'-***C***), 126.2 (2',6'-***C***), 67.6 (2-***C***), 40.9 (4-***C***), 32.0 (3-***C***), 23.6 (1-***C***), 21.3 (3',5'-C***C***H_3); GC-MS (EI) *m/z* 178 $[M]^+$, 145 $[M-(HO)CH_3]^+$, 120 $[M+H-CH_2C(H)(OH)CH_3]^+$, 105 $[M+H-(CH_2)_2C(H)(OH)CH_3]^+$; HRMS (ASAP) calculated $[M-OH]^+$ 161.1330, found $[M-OH]^+$ 161.1332.

syn-3-(3,5-Dimethylphenyl)cyclohexanol (*syn*-203)

anti-3-(3,5-Dimethylphenyl)cyclohexanol (*anti*-203)



syn-**203**



anti-**203**

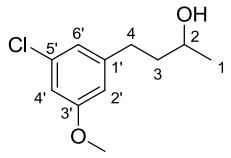
general	reaction times (min)		^{1}H NMR ratio	isolated yield (%)	
procedure	C-H borylation	1,4-conjugate addition	*syn*:*anti*	*syn*-**203**	*anti*-**203**
J (Schlenk)	60	80	1:1	29	29
K (array)	60	80	1:1	17	16

Flash column chromatography: 0-50% MTBE/cyclohexane

syn-**203**: Colourless oil; ν_{max} (neat) 3344, 2924, 2860, 1602, 1448, 1118, 974, 842, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 3H, 2',4',6'-C***H***), 4.23-4.25 (m, 1H, 1-C***H***), 2.90-2.98 (m, 1H, 3-C***H***), 2.31 (s, 6H, 3',5'-CC***H***$_3$), 1.41-1.97 (m, 9H, 2,4,5,6-C***H***$_2$+O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (1'-***C***), 137.8 (3',5'-***C***), 127.6 (4'-***C***), 124.8 (2',6'-***C***), 66.9 (1-***C***), 40.6 (3-***C***), 37.4 (2-***C***), 33.8 (6-***C***), 32.4 (4-***C***), 21.4 (C***C***H$_3$), 20.5 (5-***C***); GC-MS (EI) m/z 204 [M]$^+$, 186, 171, 157, 143, 131, 119; HRMS (ASAP) calculated [M+H]$^+$ 205.1592, found [M+H]$^+$ 205.1573.

anti-**203**: Colourless oil; ν_{max} (neat) 3344, 2928, 2854, 1604, 1448, 1364, 1056, 840, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H, 4'-C***H***), 6.85 (s, 2H, 2',6'-C***H***), 3.69-3.77 (m, 1H, 1-C***H***), 2.49-2.57 (m, 1H, 3-C***H***), 2.31 (s, 6H, 3',5'-CC***H***$_3$), 1.22-2.17 (m, 9H, 2,4,5,6-C***H***$_2$+O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.20 (1'-***C***), 137.86 (3',5'-***C***), 127.78 (4'-***C***), 124.63 (2',6'-***C***), 71.06 (1-***C***), 43.26 (3-***C***), 42.66 (2-***C***), 35.37 (6-***C***), 33.48 (4-***C***), 24.51 (C***C***H$_3$), 21.36 (5-***C***); GC-MS (EI) m/z 204 [M]+, 171, 145, 132, 119; HRMS (ASAP) calculated [M+H]$^+$ 205.1592, found [M+H]$^+$ 205.1588.

4-(3-Chloro-5-methoxyphenyl)butan-2-ol (185)



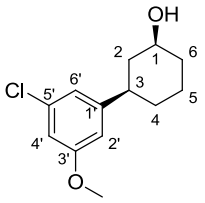
general	reaction times (min)		isolated
procedure	C-H borylation	1,4-conjugate addition	yield (%)
J (Schlenk)	20	80	71
K (array)	60	80	68

Flash column chromatography: 0-50% MTBE/cyclohexane

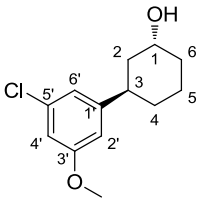
Colourless oil; ν_{max} (neat) 3350, 2964, 2924, 2864, 1574, 1458, 1430, 1272, 1150, 1050, 838, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (m, 1H, 2'-C***H***), 6.74 (m, 1H, 4'-C***H***), 6.64 (m, 1H, 6'-C***H***), 3.79 (s, 3H, OC***H***$_3$), 3.79-3.85 (m, 1H, 2-C***H***), 2.59-2.76 (m, 2H, 4-C***H***$_2$), 1.72-1.78 (m, 2H, 3-C***H***$_2$), 1.23-1.26 (m, 4H, O***H***+1-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (5'-***C***), 145.0 (1'-***C***), 134.6 (5'-***C***), 121.0 (2'-***C***), 112.9 (4'-***C***), 111.5 (6'-***C***), 67.30 (2-***C***), 55.4 (O***C***H_3), 40.4 (3-***C***), 32.0 (1-***C***), 29.7 (4-***C***), 23.8 (3',5'-C***C***H_3); GC-MS (EI) *m/z* 216 ($[M]^+$, ^{37}Cl), 214 ($[M]^+$, ^{35}Cl), 158 ($[M\text{-}CH_2C(H)(OH)CH_3]^+$, ^{37}Cl), 156 ($[M\text{-}CH_2C(H)(OH)CH_3]^+$, ^{35}Cl), 121 $[M\text{-}Cl\text{-}CH_2C(H)(OH)CH_3]^+$; HRMS (ASAP) calculated $[M\text{-}OH]^+$ 197.0733, found $[M\text{-}OH]^+$ 197.0750.

syn-3-(3-Chloro-5-methoxyphenyl)cyclohexanol (_syn_-204)

anti-3-(3-Chloro-5-methoxyphenyl)cyclohexanol (_anti_-204)



syn-**204**



anti-**204**

general	reaction times (min)		^{1}H NMR ratio	isolated yield (%)	
procedure	C-H borylation	1,4-conjugate addition	*syn*:*anti*	*syn*-**204**	*anti*-**204**
J (Schlenk)	20	80	1:1.9	34	34
K (array)	60	80	1:2	35	33

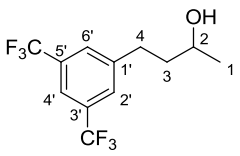
Flash column chromatography: 0-50% MTBE/cyclohexane

syn-**204**: Colourless oil; ν_{max} (neat) 3364, 2930, 2856, 1596, 1574, 1460, 1428, 1276, 1152, 1120, 1054, 976, 844, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (m, 1H, 6'-C***H***), 6.73 (m, 1H, 4'-C***H***), 6.66 (m, 1H, 2'-C***H***), 4.23-4.25 (m, 1H, 1-C***H***), 3.79 (s, 3H, OC***H***$_3$), 2.93-3.01 (m, 1H, 3-

C***H***), 1.37-1.96 (m, 9H, 2,4,5,6-C***H***$_2$+O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (3'-***C***), 150.1 (1'-***C***), 134.6 (5'-***C***), 119.5 (4'-***C***), 111.7 (6'-***C***), 111.5 (2'-***C***), 66.6 (1-***C***), 55.4 (O***C***H$_3$), 40.2 (3-***C***), 37.6 (2-***C***), 33.5 (6-***C***), 32.4 (4-***C***), 20.3 (5-***C***); GC-MS (EI) *m/z* 242 ([M]$^+$, ^{37}Cl), 240 ([M]$^+$, ^{35}Cl), 224 ([M-H_2O]$^+$, ^{37}Cl), 222 ([M-H_2O]$^+$, ^{35}Cl), 207, 205, 184 [M-$CH_2C(H)(OH)CH_2$]$^+$, ^{37}Cl), 182 [M-$CH_2C(H)(OH)CH_2$]+, ^{35}Cl), 171 ([M-$CHCH_2C(H)(OH)CH_2$]$^+$, ^{37}Cl), 169 ([M-$CHCH_2C(H)(OH)CH_2$]$^+$, ^{35}Cl), 158, 156; HRMS (ASAP) calculated [M+H]$^+$ 241.0999, found [M+H]$^+$ 241.0995.

anti-**204**: Colourless oil; ν_{max} (neat) 3374, 2926, 2854, 1598, 1574, 1458, 1428, 1276, 1152, 1120, 1056, 974, 844, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (m, 1H, 6'-C***H***), 6.74 (m, 1H, 4'-C***H***), 6.65 (m, 1H, 2'-C***H***), 3.79 (s, 3H, OC***H***$_3$), 3.69-3.76 (m, 1H, 1-C***H***), 2.50-2.58 (m, 1H, 3-C***H***), 1.21-2.18 (m, 9H, 2,4,5,6-C***H***$_2$+O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (3'-***C***), 149.1 (1'-***C***), 134.7 (5'-***C***), 119.5 (4'-***C***), 111.6 (6'-***C***), 111.5 (2'-***C***), 70.8 (1-***C***), 55.4 (O***C***H$_3$), 42.9 (3-***C***), 42.7 (2-***C***), 35.2 (6-***C***), 33.1 (4-***C***), 24.3 (5-***C***); GC-MS (EI) *m/z* 242 ([M]$^+$, ^{37}Cl), 240 ([M]$^+$, ^{35}Cl), 224 ([M-H_2O]$^+$, ^{37}Cl), 222 ([M-H_2O]$^+$, ^{35}Cl), 207, 205, 184 [M-$CH_2C(H)(OH)CH_2$]$^+$, ^{37}Cl), 182 [M-$CH_2C(H)(OH)CH_2$]+, ^{35}Cl), 171 ([M-$CHCH_2C(H)(OH)CH_2$]$^+$, ^{37}Cl), 169 ([M-$CHCH_2C(H)(OH)CH_2$]$^+$, ^{35}Cl), 158, 156; HRMS (ASAP) calculated [M+H]$^+$ 241.0995, found [M+H]$^+$ 241.0981.

4-(3,5-Bis(trifluoromethyl)phenyl)butan-2-ol (205)



general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	20	80	53
K (array)	60	80	47

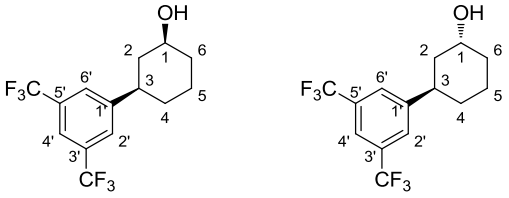
Flash column chromatography: 0-50% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 3360, 2974, 292, 1380, 1274, 1168, 1122, 890, 706, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H, 4'-C***H***), 7.67 (s, 2H, 2',6'-C***H***), 3.82-3.90 (m, 1H, 2-C***H***),

2.79-2.98 (m, 2H, 4-C***H***$_2$), 1.77-1.83 (m, 2H, 3-C***H***$_2$), 1.35-1.36 (d, 1H, O***H***), 1.27-1.28 (d, 3H, 1-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (1'-***C***), 131.6 (q, $^2J_{C\text{-}F}$ = 33, 3',5'-***C***), 128.6 (m, 2',6'-***C***), 123.4 (q, $^1J_{C\text{-}F}$ = 273, ***C***F_3), 119.9 (m, 4'-***C***), 67.1 (2-***C***), 40.3 (4-***C***), 31.8 (3-***C***), 23.9 (1-***C***); ^{19}F NMR (376 MHz, $CDCl_3$) δ 63.29; GC-MS (EI) *m/z* 268 $[M\text{-}H_2O]^+$, 253 $[M\text{-}H_2O\text{-}CH_3]^+$, 227 $[M\text{-}CH_2C(H)(OH)CH_3]^+$, 199 $[M\text{-}CF_3]^+$; HRMS (ASAP) calculated $[M\text{-}H_2O]^+$ 268.0687, found $[M\text{-}H_2O]^+$ 268.0660.

syn-3-(3,5-Bis(trifluoromethyl)phenyl)cyclohexanol (_syn_-206)

anti-3-(3,5-Bis(trifluoromethyl)phenyl)cyclohexanol (_anti_-206)



syn-**206** *anti*-**206**

general	reaction times (min)		^{1}H NMR ratio	isolated yield (%)	
procedure	C-H borylation	1,4-conjugate addition	*syn*:*anti*	*syn*-**206**	*anti*-**206**
J (Schlenk)	20	80	1:1.7	25	27
K (array)	60	80	1:1.7	23	21

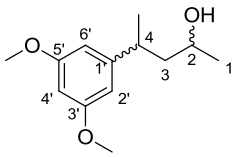
Flash column chromatography: 0-50% MTBE/cyclohexane

syn-**206**: Colourless oil; ν_{max} (neat) 3346, 2934, 2858, 1382, 1366, 1274, 1168, 1124, 976, 928, 900, 894,706, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H, 4'-C***H***), 7.67 (s, 2H, 2',6'-C***H***), 4.29-4.30 (m, 1H, 1-C***H***), 3.16-3.24 (m, 1H, 3-C***H***), 1.43-2.03 (m, 8H, 2,4,5,6-C***H***$_2$), 1.37-1.38 (d, 1H, O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (1'-***C***), 131.5 (q, $^2J_{C\text{-}F}$ = 33, 3',5'-***C***), 127.2 (2',6'-***C***), 123.5 (q, $^1J_{C\text{-}F}$ = 274, 3',5'-C***C***F_3), 120.1 (4'-***C***), 66.3 (1-***C***), 40.1 (3-***C***), 37.5 (2-***C***), 33.4

(6-***C***), 32.4 (4-***C***), 20.1 (5-***C***); ^{19}F NMR (376 MHz, $CDCl_3$) δ 63.3; GC-MS (EI) *m/z* 294 $[M\text{-}H_2O]^+$, 279, 240 $[M\text{-}(CH_2)_3C(H)OH]^+$; HRMS (ASAP) calculated $[M]^+$ 312.0949, found $[M]^+$ 312.0952.

anti-**206**: Colourless oil; ν_{max} (neat) 3346, 2932, 2862, 1382, 1360, 1274, 1168, 1124, 1056, 898, 844, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H, 4'-C***H***), 7.67 (s, 2H, 2',6'-C***H***), 3.74-3.82 (m, 1H, 1-C***H***), 2.72-2.79 (m, 1H, 3-C***H***), 1.26-2.23 (m, 9H, 2,4,5,6-CH_2+O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.41 (1'-***C***), 131.65 (q, $^2J_{C\text{-}F}$ = 33, 3',5'-***C***), 127.08 (2',6'-***C***), 123.43 (q, $^1J_{C\text{-}F}$ = 274, 3',5'-C***C***F_3), 120.28 (4'-***C***), 70.52 (1-***C***), 42.63 (3-***C***), 42.49 (2-***C***), 35.11 (6-***C***), 33.12 (4-***C***), 24.20 (5-***C***); ^{19}F NMR (376 MHz, $CDCl_3$) δ 63.27; GC-MS (EI) *m/z* 312 $[M]^+$, 294 $[M\text{-}H_2O]^+$, 279, 269 $[M\text{-}CHC(H)OH]^+$, 240 $[M\text{-}(CH_2)_3C(H)OH]^+$; HRMS (ASAP) calculated $[M]^+$ 312.0949, found $[M]^+$ 312.0940.

4-(3,5-Dimethoxyphenyl)pentan-2-ol (207) (1:1.1 mixture of diastereoisomers)

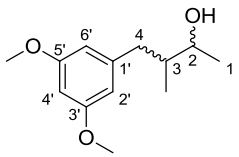


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	20	120	51
K (array)	20	120	57

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 3366, 2958, 2916, 2848, 1594, 1460, 1428, 1204, 1150, 1058, 928, 828, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38-6.39 (m, 2H, 2',6'-C***H***), 6.31-6.33 (m, 1H, 4'-C***H***), 3.58-3.83 (m, 7H, OCH_3, 2-C***H***), 2.87-2.96 (m, 1H, 4-C***H***, diastereomer A), 2.77-2.84 (m, 1H, 4-C***H***, diastereomer B), 1.59-1.85 (m, 2H, 3-CH_2), 1.13-1.30 (m, 7H, 3',5'-OCH_3, O*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 160.8, 149.8, 149.5, 105.3, 105.0, 97.8, 97.6, 66.46, 65.9, 55.3, 47.7, 47.4, 37.4, 37.0, 24.2, 23.8, 23.0, 22.2; GC-MS (EI) *m/z* 224 $[M]^+$, 166 $[M\text{-}H_2O\text{-}(CH_2)_3CH]^+$; HRMS (ES) calculated $[M+H]^+$ 225.1491, found $[M+H]^+$ 225.1475.

4-(3,5-Dimethoxyphenyl)-3-methylbutan-2-ol (208) (1:1 mixture of diastereoisomers)

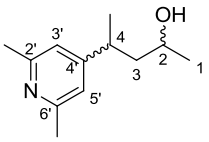


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	20	120	52
K (Array)	20	120	47

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 3388, 2962, 2930, 2840, 1594, 1460, 1428, 1204, 1150, 1058, 928, 828, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.38-6.39 (m, 2H, 2',6'-C***H***), 6.31-6.33 (m, 1H, 4'-C***H***), 3.58-3.83 (m, 7H, 2-C***H***, OC***H***$_3$), 2.87-2.96 (m, 2H, 3-C***H***$_2$, diastereomer A), 2.76-2.85 (m, 2H, 3-C***H***$_2$, diastereomer B), 1.58-1.85 (m, 2H, 4-C***H***$_2$), 1.13-1.29 (m,7H, 1-C***H***$_3$, 3-CC***H***$_3$, O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 160.8, 149.8, 149.4, 105.3, 105.0, 97.8, 97.6, 66.5, 65.9, 55.3, 47.7, 47.4, 37.4, 37.0, 24.2, 23.8, 23.0, 22.2; GC-MS (EI) *m/z* 224 $[M]^+$, 179 $[M\text{-}H_2O\text{-}(CH_2)_2CH]^+$, 166 $[M\text{-}H_2O\text{-}(CH_2)_3CH]^+$; HRMS (ES) calculated $[M+H]^+$ 225.1491, found $[M+H]^+$ 225.1477.

4-(2,6-Dimethylpyridin-4-yl)pentan-2-ol (209) (1:1 mixture of diastereoisomers)



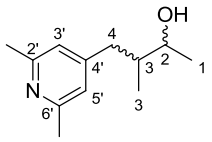
general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	5	120	38
K (array)	20	120	30

Flash column chromatography: 0-100% EtOAc/cyclohexane

Colourless oil; ν_{max} (neat) 3374, 2926, 2854, 1598, 1574, 1458, 1428, 1276, 1152, 1120, 1056, 974, 844, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, 3',5'-C***H***), 3.74-3.82 (m, 1H, 2-C***H***, diastereomer A), 3.49-3.57 (m, 1H, 2-C***H***, diastereomer B), 2.86-2.95 (m, 1H, 4-C***H***,

diastereomer B), 2.76-2.85 (m, 1H, 4-C***H***, diastereomer A), 2.49 (s, 6H, 2',6'-CC***H***$_3$), 1.57-1.82 (m, 2H, 4-C***H***$_2$), 1.14-1.25 (m, 5H, 1-C***H***$_3$, 4-CC***H***$_3$, O***H***), 1.20-1.23 (m, 4H, 1-C***H***$_3$+O***H***), 0.82-0.87 (m, 3H, 3-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 157.7, 156.9, 156.4, 119.2, 118.2, 65.9, 46.9, 46.9, 36.0, 36.0, 24.4, 24.4, 23.9, 22.4, 21.3; LC-MS (ES) *m/z* 194 $[M+H]^+$; HRMS (ES) calculated $[M+H]^+$ 194,1545, found $[M+H]^+$ 194.1541.

4-(2,6-Dimethylpyridin-4-yl)-3-methylbutan-2-ol (210) (1:1.1 mixture of diastereoisomers)

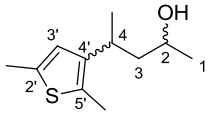


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	5	120	36
K (array)	20	120	25

Flash column chromatography: 0-25% MeOH/DCM

Colourless oil; ν_{max} (neat) 3322, 2962, 2928, 1608, 1566, 1458, 1428, 1376, 1130, 1038, 1006, 922, 864 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 2H, 3',5'-C***H***), 3.73-3.79 (m, 1H, 2-C***H***, diastereomer A), 3.64-3.70 (m, 1H, 2-C***H***, diastereomer B), 2.73-2.86 (m, 2H, 4-C***H***$_2$), 2.49 (s, 6H, 2',6'-CC***H***$_3$), 2.22-2.33 (m, 1H, 4-C***H***), 1.76-1.84 (m, 1H, 3-C***H***), 1.20-1.23 (m, 4H, 1-C***H***$_3$+O***H***), 0.82-0.87 (m, 3H, 3-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 150.7, 121.2, 41.6, 41.0, 38.5, 38.3, 24.4, 20.5, 20.2, 14.8, 13.6; LC-MS (ES) *m/z* 194 $[M+H]^+$; HRMS (ES) calculated $[M+H]^+$ 194.1545, found $[M+H]^+$ 194.1540.

4-(2,5-Dimethylthiophen-3-yl)pentan-2-ol (211) (1:1 mixture of diastereoisomers)

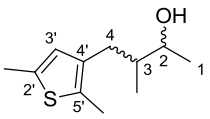


general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	20	120	41
K (array)	20	120	36

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; ν_{max} (neat) 3358, 2958, 2918, 2870, 1450, 1374, 1220, 1140, 1024, 948, 826, 676, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 1H, 3'-C***H***, enantiomer A), 6.47 (s, 1H, 3'-C***H***, diastereomer B), 3.73-3.81 (m, 1H, 2-C***H***, enantiomer A), 3.53-3.61 (m, 1H, 2-C***H***, diastereomer B), 2.98-3.07 (m, 1H, 4-C***H***, diastereomer B), 2.86-2.95 (m, 1H, 4-C***H***, diastereomer A), 2.32-2.39 (m, 6H, 2',5'-CC***H***$_3$), 1.59-1.76 (m, 2H, 3-C***H***$_2$) 1.25-1.35 (m, 1H, O***H***), 1.14-1.18 (m, 6H, 4-CC***H***$_3$, 1-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 141.8, 135.9, 135.5, 129.9, 129.4, 124.0, 123.8, 67.0, 66.2, 47.4, 47.2, 30.2, 29.4, 26.9, 24.3, 23.7, 22.4, 21.9, 15.3, 12.7; LC-MS (ES) *m/z* 199 $[M+H]^+$, 181 $[M+H-F]^+$; HRMS (ES) calculated $[M+H]^+$ 199.1157, found $[M+H]^+$ 199.1144.

4-(2,5-Dimethylthiophen-3-yl)-3-methylbutan-2-ol (212) (1:1 mixture of diastereoisomers)



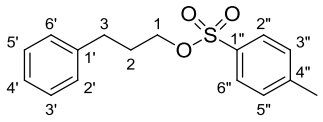
general procedure	reaction times (min)		isolated yield (%)
	C-H borylation	1,4-conjugate addition	
J (Schlenk)	20	120	47
K (Array)	20	120	43

Flash column chromatography: 0-25% MTBE/cyclohexane

Colourless oil; FT-IR (neat) 3362, 2968, 2916, 2880, 1450, 1376, 1216, 1140, 1092, 1000, 928, 896, 828, 494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 1H, 3'-C***H***), 3.66-3.79 (m, 1H, 2-C***H***), 2.57-2.66 (m, 1H, 4-C***H***), 2.39 (s, 3H, 2'-CC***H***$_3$), 2.30 (m, 3H, 5'-CC***H***$_3$), 2.23-2.32 (m, 1H, 4-C***H***), 1.68-1.79 (m, 1H, 3-C***H***), 1.20 (d, *J* = 8, 3H, 1-C***H***$_3$), 0.84-0.89 (m, 3H, 4-CC***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 136.1, 134.9, 130.9, 127.4, 119.6, 71.6, 70.4, 41.8, 41.0, 31.6, 31.4, 20.6, 19.9, 15.1, 15.0, 13.6, 13.0; LC-MS (ES) *m/z* 199 $[M+H]^+$, 181 $[M+H-F]^+$; $[M-H_2O-(CH_2)_3CH]^+$; HRMS (ES) calculated $[M+H]^+$ 199.1157, found $[M+H]^+$ 199.1141.

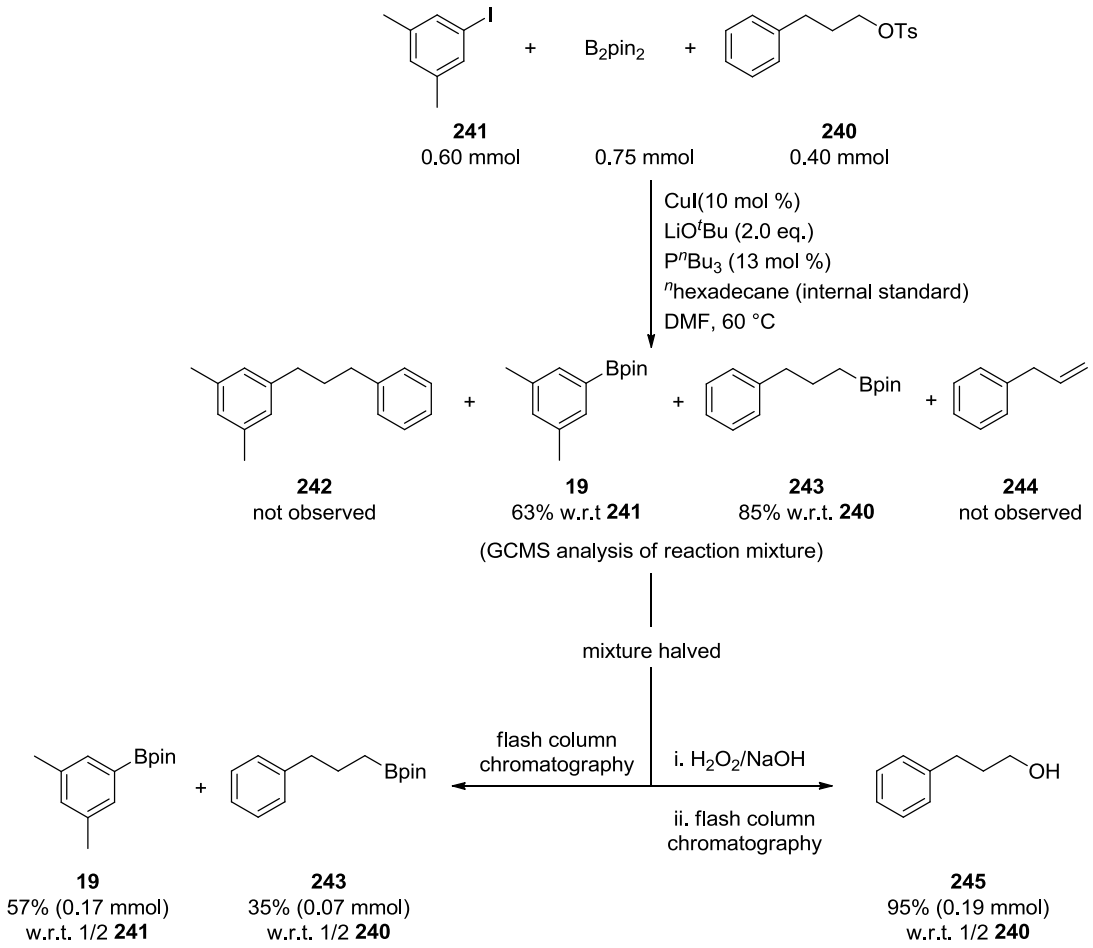
Copper-Catalysed Borylation of Alkyl Halides: Mass Balance Study

3-Phenylpropyl 4-methylbenzenesulfonate (240)



General procedure P was applied to 3-phenylpropan-1-ol (**239**) (1.36g, 10 mmol). Purification by flash column chromatography (0-50% EtOAc/hexane) afforded 3-phenylpropyl 4-methylbenzenesulfonate (**240**) (2.47 g, 85%); ν_{max} 2942, 1742, 1502, 1453, 1355, 1173, 1094, 992, 925, 813, 702, 661, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2, 2H, 2'',6''-C***H***), 7.37 (d, *J* = 8.2, 2H, 3'',5''-C***H***), 7.25-7.28 (m, 2H, 3',5'-***H***), 7.18-7.22 (m, 1H, 4'-C***H***), 7.08-7.10 (m, 2H, 2',6'-C***H***), 4.06 (t, *J* = 6.0, 2H, 1-C$\mathbf{H_2}$), 2.67 (t, *J* = 7.6, 2H, 3-C$\mathbf{H_2}$), 2.48 (s, 3H, C$\mathbf{H_3}$), 1.95-2.02 (m, 2H, 2-C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (***C***-1''), 140.5 (***C***-1'), 133.3 (***C***-4''), 130.0 (***C***-3'',5''), 128.6 (***C***-2',6'), 128.5 (***C***-5',3'), 128.0 (***C***-2'',3''), 126.3 (***C***-4'), 69.7 (***C***-1), 31.6 (***C***-3), 30.6 (***C***-2), 21.8 (***C***H_3); ASAP (ES) *m*/*z* 290 $[M]^+$.

Mass-Balance Study



A solution of 3-phenylpropyl 4-methylbenzenesulfonate (**240**) (116 mg, 0.40 mmol) in DMF (0.6 mL) was added to a mixture of CuI (11 mg, 10 mol%), LiO^{t}Bu (160 mg, 1.2 mmol) and B_2pin_2 (190 mg, 0.75 mmol). *m*-Xylyliodide (**241**) (87 µL, 0.60 mmol), and P^{n}Bu$_3$ (19 µL, 13 mol%) were then added successively by syringe and the resultant mixture was stirred vigorously on a preheated metal block at 60 °C for 24 h. The reaction mixture was diluted with H_2O (20 ml), extracted with Et_2O (3x15 ml) and the combined organics dried over $MgSO_4$. GC-MS analysis of the mixture calibrated against purified samples of *m*-xylylBpin (**19**) and 3-phenylpropyl-1-Bpin (**243**) with ^{n}dodecane as internal standard [***Note 1***] showed complete consumption of the starting tosylate (**241**) [***Note 2***] and 63% and 85% yields [***Note***

3] of *m*-xylylBpin (**19**) and 3-phenylprop-1-ylBpin (**243**), respectively. Half of the mixture was concentrated under reduced pressure and purified using silica gel flash chromatography (0-20% EtOAc in petrol) to give **19** and **243** in 57% and 35% yields, respectively [***Note 4***]. The other half of the mixture was concentrated under reduced pressure, diluted with THF (1.0 mL) followed by successive additions of aq. NaOH (2.0 M, 0.6 ml, 1.2 mmol) and aq. H_2O_2 (27.5% wt., 0.6 mL). After 2 hours, TLC showed complete consumption of both *m*-xylylBpin (**19**) and 3-phenylpropyl-1-Bpin (**243**). The mixture was treated with 5.0 mL saturated aq. $Na_2S_2O_3$ and stirred for another 10 minutes. The mixture was acidified using aq. HCl (1.0 M, 5.0 mL), extracted with EtOAc (3x10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash column chromatography (0-50% EtOAc in petrol) afforded 3-phenylpropan-1-ol (**245**) in 95% yield.

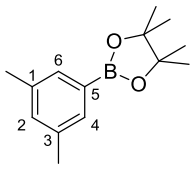
[***Note 1***] Calibration of GC-MS was carried out using 3:1, 2:1, 1:1, 1:2 and 1:3 mixtures of purified samples of *m*-xylylBpin (**19**) or 3-phenylpropyl-1-Bpin (**243**) and ^{n}hexadecane.

[***Note 2***] No evidence for the formation of 3-phenylpropan-1-ol (**245**) could be observed at this stage.

[***Note 3***] Yield of *m*-xylylBpin (**19**) with respect to 0.60 mmol *m*-xylyliodide (**240**). Yield of 3-phenylprop-1-ylBpin (**243**) with respect to 0.40 mmol 3-phenylprop-1-yltosylate (**241**).

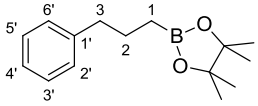
[***Note 4***] Yield of *m*-xylylBpin (**19**) with respect to 0.30 mmol *m*-xylyliodide (**240**). Yield of 3-phenylprop-1-ylBpin (**243**) with respect to 0.20 mmol 3-phenylprop-1-yltosylate (**241**).

2-(3,5-Dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (19)[10]



Prepared following experimental procedure described for mass balance study. Colourless solid; m.p. 97.1-98.0 °C; ν_{max} (neat) 2991 , 2976, 2359, 2338, 1599, 1420, 1356, 1240, 1139, 964, 849, 711 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 2H, 4,6-C***H***), 7.11 (s, 1H, 2-C***H***), 2.32 (s, 6H, 1,3-C***H***$_3$), 1.35 (s, 12H, pin-C(C***H***$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3 (***C***-1,3), 133.2 (***C***-4,6), 132.5 (***C***-2), 83.8 (pin-***C***$(CH_3)_2$), 25.0 (pin-C(***C***$H_3)_2$), 21.3 (1,3-C***C***H_3); ^{11}B NMR (128 MHz, $CDCl_3$) *δ* 31.00; GC-MS (EI) *m/z* 232 $[M]^+$, 217 $[M\text{-}CH_3]^+$, 190 $[M\text{-}C(CH_3)_2]^+$, 175, 159, 146 $[M\text{-}C_2(CH_3)_4]^+$, 133 $[M\text{-}C(CH_3)_2C(CH_3)_2O]^+$.

4,4,5,5-Tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (243)[11]

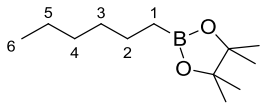


Prepared following experimental procedure described for mass balance study. Purification by flash column chromatography (24 g column, 0-100% DCM/hexane, 26 column volumes) afforded 4,4,5,5-tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (**243**) as colourless solid; m.p. 32.2-33.4 °C; ν_{max} 2980, 1376, 1322, 1145, 966, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.28 (m, 2H, 3',5'-***H***), 7.14-7.18 (m, 3H, 2',4',6'-***H***), 2.61 (t, *J* = 7.6, 2H, 3-C***H***$_2$), 1.69-1.77 (m, 2H, 2-C***H***$_2$), 1.24 (s, 12H, pin-CC***H***$_3$), 0.83 (t, *J* = 7.8, 2H, 1-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (***C***-1'), 128.7 (***C***-3',5'), 128.3 (***C***-2',6'), 125.7 (***C***-4'), 83.1 (pin-***C***CH_3), 38.8 (***C***-3), 26.2 (pin-C***C***H_3), 25.0 (***C***-2); ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.98; GC-MS (EI) *m/z* 246

$[M]^+$, 118 $[M\text{-Bpin}]^+$, 91 $[M\text{-}(CH_2)_2\text{Bpin}]^+$; HRMS (ASAP) m/z calculated $[M]^+$ 246.1786, found $[M]^+$ 246.1789.

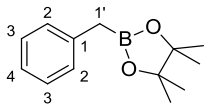
Copper-Catalysed Borylation of Alkyl Halides and Pseudo-Halides

2-Hexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (238)[12]



General Procedure L was applied to 1-bromohexane (**236**) (165 mg, 1.0 mmol). Purification by flash column chromatography (24 g column, 0-100% DCM/hexane, 26 column volumes) afforded 2-hexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**239**) as colourless liquid (151 mg, 71%); ν_{max} 2982, 2923, 2857, 1372, 1320, 1146, 974, 847, 543; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.40 (m, 2H, 5-C***H***$_2$), 1.24-1.30 (m, 6H, 2,3,4-C***H***$_2$), 1.24 (s, 12H, pin-CC***H***$_3$), 0.87 (t, *J* = 7.2, 3H, 6-C***H***$_3$), 0.77 (t, *J* = 7.6, 2H, 1-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.0 (pin-***C***CH_3), 32.2 (***C***-4), 31.8 (***C***-3), 25.0 (pin-C***C***H_3), 24.1 (***C***-2), 22.7 (***C***-5), 14.3 (***C***-6); ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.1; GC-MS (EI) *m/z* 212 [M]+, 197 [M-CH_3]$^+$, 129 [M-$HC(CH_3)_2C(CH_3)_2$]$^+$; HRMS (ASAP) *m/z* calculated [M]$^+$ 212.1948, found [M]$^+$ 212.1949.

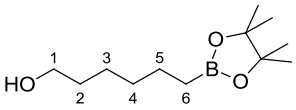
2-Benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (260)[13]



General Procedure L was applied to (bromomethyl)benzene (171 mg, 1.0 mmol). Purification by flash column chromatography (24 g column, 0-100% DCM/hexane, 26 column volumes) afforded 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**260**) as colourless liquid (155 mg, 71%). ν_{max} 2977, 2920, 1327, 1140, 966, 845, 696, 536 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.19 (m, 5H, 2,3,4,5,6-C***H***), 2.29 (s, 2H, 1'-C***H***$_2$), 1.29 (s, 12H, pin-CC***H***$_3$); ^{13}C NMR (101

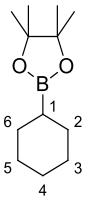
MHz, $CDCl_3$) δ 138.8 (***C***-1), 129.1, 128.4, 125.0, 83.6 (pin-***C***CH_3), 24.89 (pin-C***C***H_3); ^{11}B NMR (128 MHz, $CDCl_3$,) δ 33.20; GC-MS (EI) m/z 218 $[M]^+$, 203 $[M\text{-}CH_3]^+$, 203 $[M\text{-}(CH_3)_2]^+$, 132, 118 $[M\text{-}(CCH_3)_2O]^+$; HRMS (ASAP) *m*/*z* calculated $[M]^+$ 218.1478, found $[M]^+$ 218.1475.

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-ol (265)



General Procedure L was applied to 6-bromohexan-1-ol (181 mg, 1.0 mmol). Purification by flash column chromatography (24 g column, 0-30% ether/hexane, 26 column volumes) afforded 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-ol (**265**) as colourless liquid (110 mg, 48%). ν_{max} 3392 (br), 2980, 2927, 2862, 1371, 1318, 1143, 1054, 964, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.4, 2H, 1-C***H***$_2$), 1.52-1.55 (m, 3H, O***H***+2-C***H***$_2$), 1.29-1.41 (m, 6H, 3,4,5-C***H***$_2$), 1.22 (s, 12H, pin-CC***H***$_3$), 0.75 (t, *J* = 7.6, 2H, 6-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.0 (pin-***C***CH_3), 63.1 (***C***-1), 32.8 (***C***-2), 32.1 (***C***-4), 25.6 (***C***-3), 24.9 (pin-C***C***H_3), 24.0 (C-***5***; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0; ASAP (ES) *m*/*z* 228 $[M]^+$; HRMS (ASAP) *m*/*z* calculated $[M]^+$ 228.1897, found $[M]^+$ 228.1895.

2-Cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (270)[14]

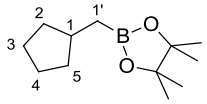


General Procedure L was applied to bromocyclohexane (163 mg, 1.0 mmol) at elevated temperature (37 ˚C) and extended reaction time (24 h). Purification by flash column chromatography (24 g column, 0-100% DCM/hexane, 26 column volumes) afforded 2-

cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**270**) as colourless liquid (137 mg, 79%). Identical yield was obtained from the borylation of iodocyclohexane (210 mg, 1.0 mmol) under general procedure B; ν_{max} 2986, 2924, 2844, 1380, 1312, 1150, 1005, 967, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.68 (m, 6H), 1.28-1.38 (m, 4H), 1.23 (s, 12H, pin-CC***H***$_3$), 0.97-1.00 (m, 1H, 1-C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.9 (pin-***C***CH_3), 28.1, 27.3, 26.9, 24.9 (pin-C***C***H_3); ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.1; GC-MS (EI) *m/z* 210 $[M]^+$, 195 $[M-CH_3]^+$, 124; HRMS (ASAP) calculated $[M]^+$ 210.1791, found $[M]^+$ 210.1796.

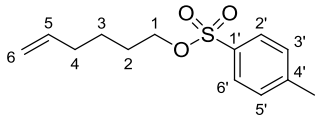
Hexenyl-Halide and Pseudo-Halide Experiments

2-(Cyclopentylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (280)[15]



General Procedure L was applied to 6-bromohex-1-ene (**278**) (163 mg, 1.0 mmol). Purification by flash column chromatography (24 g column, 0-100% DCM/hexane, 26 column volumes) afforded 2-(cyclopentylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**280**) as colourless liquid (120 mg, 57%); ν_{max} 2982, 2946, 2870, 1389, 1312, 1143, 964, 848, 733; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89-1.99 (m, 1H, 1-C***H***), 1.74-1.82 (m, 2H), 1.58-1.64 (m, 2H), 1.48-1.53 (m, 2H), 1.24 (s, 12H, pin-CC***H***$_3$), 1.01-1.10 (m, 2H) 0.84 (d, *J* = 7.6, 2H, 1'-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.0 (pin-***C***CH_3), 36.3 (***C***-2,5), 35.2 (***C***-3,4), 25.3 (***C***-1), 25.0 (pin-C***C***H_3); ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.8; GC-MS (EI) *m/z* 210 $[M]^+$, 195 $[M\text{-}CH_3]^+$, 129; HRMS (ASAP) *m/z* calculated $[M]^+$ 210.1791, found $[M]^+$ 210.1795.

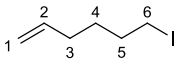
Hex-5-en-1-yl 4-methylbenzenesulfonate (282)[16]



General procedure P was applied to hex-5-en-1-ol (**281**) (1.00g, 10.0 mmol). Purification by flash column chromatography (0-50% EtOAc/hexane) afforded hex-5-en-1-yl 4-methylbenzenesulfonate (**282**) as colourless liquid (1.81 g, 71%); ν_{max} 2938, 2854, 1597, 1360, 1173, 1097, 938, 808, 728, 666, 553 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2H, *J* = 8.4, 2',6'-C***H***), 7.34 (d, *J* = 8.0, 2H, 3',5'-C***H***), 5.67-5.77 (m, 1H, 5-C***H***), 4.92-4.99 (m, 2H, C***H***$_2$),

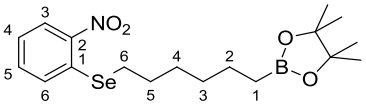
4.03 (t, *J* = 6.4, 2H, 1-C***H***$_2$), 2.45 (s, 3H, C***H***$_3$), 1.98-2.03 (m, 2H, 4-C***H***$_2$), 1.62-1.67 (m, 2H, 2-C***H***$_2$), 1.37-1.45 (m, 2H, 3-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (***C***-1'), 138.0 (***C***-4'), 133.5 (***C***-5), 129.9 (***C***-3',5'), 128.0 (***C***-2',6'), 115.2 (***C***-6), 70.55 (***C***-1), 33.1 (***C***-4), 28.4 (***C***-2), 24.7 (C-***3***), 21.8 (***C***H_3); ASAP (ES) *m/z* 254 $[M]^+$.

1-Iodohexane (283)[16]



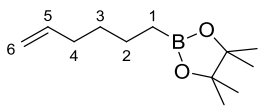
In air, I_2 (5.08 g, 20.0 mmol) was added portion-wise to an ice-cooled mixture of triphenylphosphine (5.24 g, 20.0 mmol), hex-5-en-1-ol (**281**) (1.00 g, 10.0 mmol) and imidazole (1.36 g, 20.0 mmol) in ether/acetonitrile (4:1, 250 mL). The reaction mixture was stirred for 4 hours, concentrated under reduced pressure and triturated with hexane. The resultant liquor was washed with saturated aq. $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (24 g column, 0-100% DCM/hexane, 24 column volumes) afforded 1-iodohexane (**283**) as colourless liquid (2.06 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.84 (m, 1H, 2-C***H***), 4.95-5.05 (m, 2H, 1-C***H***$_2$), 3.19 (t, *J* = 6.8, 2H, 6-C***H***$_2$), 2.05-2.11 (m, 2H, 3-C***H***$_2$), 1.81-1.88 (m, 2H, 5-C***H***$_2$), 1.47-1.54 (m, 2H, 4-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (***C***-2), 115.1 (***C***-1), 33.1 (***C***-3), 32.8 (***C***-4), 92.9 (***C***-5), 6.85 (***C***-6); GC-MS (EI) *m/z* 210 $[M]^+$, 155 $[M-CH_2CHCH_2CH_2]^+$, 127,$[I]^+$, 83 $[M-I]^+$.

4,4,5,5-Tetramethyl-2-(6-((2-nitrophenyl)selanyl)hexyl)-1,3,2-dioxaborolane (284)



Under N_2, a P^nBu_3 (1.96 g, 9.7 mmol) was added dropwise to a solution of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-ol (**265**) (1.84 g, 8.1 mmol) and *o*-nitrophenylselenocyanate (2.2 g, 9.7 mmol) in THF (31 mL). The reaction mixture was stirred at room temperature for 18 h and concenrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (40 g column, 0-20% EtOAc/hexane, 20 column volumes) afforded 4,4,5,5-tetramethyl-2-(6-((2-nitrophenyl)selanyl)hexyl)-1,3,2-dioxaborolane (**284**) as yellow oil (80%); ν_{max} 2982, 2928, 2858, 1596, 1564, 1520, 1374, 1328, 1302, 1142, 1094, 844, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, 1H, *J* = 9.2, 3-C***H***), 7.50-7.51 (m, 2H, 4,5-C***H***), 7.27-7.31 (m, 1H, 4-C***H***), 2.90 (t, 2H, *J* = 7.6, 6-C$\underline{\boldsymbol{H}}_2$), 1.73-1.80 (m, 2H, 5-C$\underline{\boldsymbol{H}}_2$), 1.32-1.51 (m, 6H, 2,3,4-C$\underline{\boldsymbol{H}}_2$), 1.24 (s, 12H, pin-CC$\underline{\boldsymbol{H}}_3$), 0.77 (t, 2H, *J* = 7.6, 1-C$\underline{\boldsymbol{H}}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (***C***-1), 134.1 (***C***-4'), 133.6 (***C***-2'), 129.2 (***C***-3'), 126.6 (***C***-5'), 125.3 (***C***-6'), 83.05 (pin-***C***CH_3), 31.9 (***C***-4), 30.0 (***C***-6), 28.3 (***C***-3), 26.4 (***C***-5), 25.0 (pin-C***C***H_3), 23.92 (***C***-2); ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0; GC-MS (EI) *m*/*z* 415 ($[M]^+$, ^{82}Se), 413 ($[M]^+$, ^{80}Se), 411 ($[M]^+$, ^{78}Se), 410 ($[M]^+$, ^{77}Se), 409 ($[M]^+$, ^{76}Se), 407 ($[M]^+$, ^{74}Se); HRMS (ASAP) *m*/*z* calculated $[M]^+$ 413.1271, found $[M]^+$ 413.1275.

2-(Hex-5-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (279)

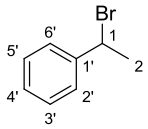


In air, *m*CPBA (<71% wt., 0.30 g, 1.7 mmol)was added to a solution of 4,4,5,5-tetramethyl-2-(6-((2-nitrophenyl)selanyl)hexyl)-1,3,2-dioxaborolane (**281**) (0.70 g, 1.7 mmol) in ether (3.0 mL) at 0 ˚C. The reaction mixture was stirred for 30 min, allowed to warm to room temperature, quenched with saturated $Na_2S_2O_3$, extracted into ether, dried over $MgSO_4$ and

concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (40 g column, 0-30% EtOAc/petrol, 20 column volumes) afforded 2-(hex-5-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**279**) as colourless oil (171 mg, 48%); ν_{max} 2977, 2924, 2858, 1371, 1316, 1148, 964, 907, 846 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76-5.86 (m, 1H, 5-C***H***), 4.89-5.01 (m, 2H, 6-C***H***$_2$), 2.01-2.07 (m, 2H, 4-C***H***$_2$), 1.37-1.44 (m, 4H, 2,3-C***H***$_2$), 1.24 (s, 12H, pin-CC***H***$_3$), 0.78 (t, 2H, *J* = 7.6, 1-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3 (***C***-5), 114.2 (***C***-6), 83.0 (pin-***C***CH_3), 33.7 (***C***-4), 31.8 (***C***-3), 25.0 (pin-C***C***H_3), 23.7 (***C***-2); ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.1; GC-MS (EI) *m*/*z* 210 $[M]^+$, 195 $[M-CH_3]^+$, 167, 153, 101; HRMS (ASAP) *m*/*z* calculated $[M]^+$ 210.1756, found $[M]^+$ 210.1755.

(1-Bromoethyl)benzene Experiments

(1-Bromoethyl)benzene (292)[17]

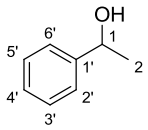


To a solution of rac-1-phenyl-1-ethanol (*rac*-**291**) (0.61g, 5.0 mmol) in hexane (25 mL) was added DMAP (1.25g, 10.0 mmol) and the reaction mixture was ice-cooled. To this was added a dropwise a solution of $POBr_3$ (0.94 g, 3.4 mmol) in hexane (6.0 mL) and the reaction mixture was stirred at room temperature for another 2 hours. The reaction mixture was filtered, washed with water, washed with saturated aq. Na_2CO_3, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography afforded *rac*-(1-bromoethyl)benzene (*rac*-**292**) (564 mg, 61%) as colourless oil; ν_{max} 3029, 2971, 2924, 1746, 1493, 1453, 1382, 1208, 1186, 1043, 1022, 968, 920, 761, 698, 592, 561 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44-7.46 (m, 2H, 2',6'-C***H***), 7.33-7.37 (m, 2H, 3',5'-C***H***), 7.27-7.31 (m, 1H, 4'-C***H***), 5.23 (q, *J* = 6.8, 1H, 1-C***H***), 2.06 (d, *J* = 7.2, 2-C$\boldsymbol{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (***C***-1'), 128.1 (***C***-2',6') 148.5 (***C***-4'), 126.9 (***C***-3',5'), 49.7 (***C***-1), 27.0 (***C***-2); ASAP (ES) *m/z* 186 ($[M]^+$, ^{81}Br), 184 ($[M]^+$, ^{79}Br); HRMS (ASAP) *m/z* calculated $[M]^+$ 183.9882, found $[M]^+$ 183.9884.

(S)-**292** was obtained in 61% yield from (R)-1-phenyl-1-ethanol [(R)-**291**)] under identical conditions; $[\alpha]_D^{23}$ = -80±7 (c = 1, $CHCl_3$).

(R)-**292** was obtained in 61% yield from (S)-1-phenyl-1-ethanol [(S)-**291**)] under identical conditions; $[\alpha]_D^{23}$ = +85±5 (c = 1, $CHCl_3$).

1-Phenyl-1-ethanol (291)



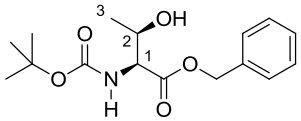
General procedure L was applied to rac-(1-bromoethyl)benzene (**292**) (185 mg, 1.0 mmol). The crude mixture was treated with a solution of oxone® in acetone/water (1:1) at room temperature for 30 minutes, quenched with saturated aq. $Na_2S_2O_3$, extracted with EtOAc, dried over $MgSO_4$ and concentrated to give another crude mixture. Purification by flash column chromatography (12 g column, 0-30% EtOAc/hexane, 24 column volumes) afforded rac-1-phenyl-1-ethanol (*rac*-**291**) as colourless oi**l** (73 mg, 60%); $[\alpha]_D$ = ca. 0; ν_{max} 3346, 2968, 1492, 1454, 1367, 1299, 1200, 1075, 1009, 897, 760, 694, 605, 542 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.39 (m, 4H, 2',3',5',6'-C***H***), 7.26-7.28 (m, 1H, 4'-C***H***), 4.86-4.92 (m, 1H, 1-C***H***), 1.50 (d, *J* = 6.8, 2-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0 (***C***-1'), 128.6 (***C***-2',6') 127.6 (***C***-4'), 125.5 (***C***-3',5'), 70.5 (***C***-1), 25.3 (***C***-2); LC-MS (ES) *m*/*z* 122 $[M]^+$; HRMS (ASAP) *m*/*z* calculated $[M+H]^+$ 123.0804, found $[M]^+$ 123.0810.

rac-1-phenyl-1-ethanol (**291**) was obtained in 60% yield from (S)-(1-bromoethyl)benzene [(S)-**291**] under identical conditions.

rac-1-phenyl-1-ethanol (**291**) was obtained in 56% yield from (R)-(1-bromoethyl)benzene [(R)-**289**] under identical conditions.

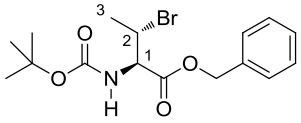
Threonine Experiments

N-Boc-L-threonine benzyl ester (303)[18]



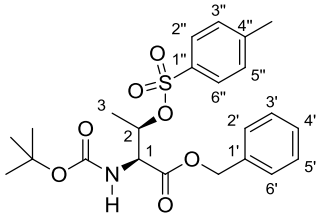
In air, Na_2CO_3 (3.18 g, 30.0 mmol) was added to a solution of N-Boc-L-threonine (**302**) (2.19 g, 10.0 mmol) in DMF (40 mL). The mixture was ice-cooled, benzyl bromide (3.42 g, 20.0 mmol) added dropwise and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was filtered through celite, diluted with water, extract with ether, washed with water then brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (40g column, 0-50% EtOAc/petrol, 12 column volumes) afforded N-boc-L-threonine benzyl ester (**303**) as colourless liquid (2.69 g, 87%); $[\alpha]_D^{23}$ = -18 ± 0.5 (c = 0.5, MeOH); ν_{max} 3426, 2975, 1720, 1689, 1499, 1368, 1157, 1070, 992, 738, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31-7.38 (m, 5H, Ar-C***H***), 5.34 (d, *J* = 7.6, 1H, N***H***), 5.16-5.24 (m, 2H, C***H***$_2$), 4.27-4.35 (m, 2H, 1,2-C***H***), 2.06-2.10 (d, *J* = 4.4, 1H, O***H***), 1.44 (s, 9H, Boc-C(C***H***$_3$)$_3$), 1.23 (d, *J* = 6.4, 3H, 3-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (1-CH***C***=O), 156.2 (NH***C***=O), 135.5 (***C***-1'), 128.8 (***C***-Ar), 128.6 (***C***-Ar), 128.3 (***C***-Ar), 68.3 (Boc-***C***$(CH_3)_3$), 67.4 (***C***H_2), 59.0 (***C***-2), 53.5 (***C***-1), 28.4 (Boc-C(***C***$H_3)_3$), 20.1 (***C***-3); GC-MS (EI) *m/z* 209 $[M\text{-Boc}]^+$, 91 $[C_6H_2CH_2]^+$.

(2R,3S)-Benzyl 3-bromo-2-((*tert*-butoxycarbonyl)amino)butanoate (304)



In air, CBr_4 (1.82 g, 5.5 mmol) was added to ice-cooled solution of PPh_3 (1.44 g, 5.5 mmol) and N-Boc-L-threonine benzyl ester (**303**) (1.55 g, 5.0 mmol) in DCM (100 mL). The reaction mixture was allowed to warm to room temperature and stirred for another 2 hours. The mixture was filtered through celite, concentrated under reduced pressure, triturated with hexane, diluted with ether, washed with water then brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography afforded (2R,3S)-benzyl 3-bromo-2-((*tert*-butoxycarbonyl)amino)butanoate (**304**) as colourless oil (1.34 g, 72%); $[\alpha]_D^{23}$ = +28 ±1 (c = 1.0, $CHCl_3$); ν_{max} 3364, 2978, 2933, 1712, 1498, 1374, 1150, 1080, 956, 912, 854, 750, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.39 (m, 5H, Ar-C***H***), 5.10 (d, *J* = 8.4, 1H, N***H***), 5.18-5.30 (m, 2H, C***H***$_2$), 4.56-4.59 (m, 1H, 1-C***H***), 4.32-4.35 (m, 1H, 2-***H***), 1.75 (d, *J* = 7.2, 3H, 3-C***H***$_3$), 1.45 (s, 9H, Boc-C(C***H***$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (1-CH***C***=O), 154.9 (NH***C***=O), 134.9 (***C***-1'), 128.6 (***C***-Ar), 128.6 (***C***-Ar), 128.5 (***C***-Ar), 67.7 (Boc-***C***$(CH_3)_3$), 59.4 (***C***-1), 49.7 (***C***H_2), 28.3 (***C***-2), 28.3 (Boc-C(***C***$H_3)_3$), 22.8 (***C***-3); GC-MS (EI) *m/z* 373 ($[M]^+$, ^{81}Br), 371 ($[M]^+$, ^{79}Br), 149.

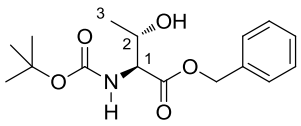
(2S,3R)-Benzyl 2-((*tert*-butoxycarbonyl)amino)-3-(tosyloxy)butanoate (308)[19]



General procedure P was applied to N-Boc-L-threonine benzyl ester (**303**) (1.55g, 5.0 mmol). Purification by flash column chromatography (0-50% ether/hexane) afforded (2S,3R)-benzyl 2-((*tert*-butoxycarbonyl)amino)-3-(tosyloxy)butanoate (**308**) as colourless oil (1.51 g, 65%); $[\alpha]_D$ = +38±4 (c=1.7, $CHCl_3$); ν_{max} 1752, 1719, 1510, 1364, 1316, 1214, 1164, 1084, 960, 906,

750, 665, 560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4, 2H, 2'',6''-C***H***), 7.30-7.41 (m, 7H, 2',3',4',5',6',3'',5''-C***H***), 5.18-5.25 (m, 2H, N***H***+2-C***H***), 4.42-4.90 (m, 2H, 1-CH_2), 2.43 (s, 3H, 4''-CCH_3), 1.43 (s, 9H, boc-C(CH_3)$_3$), 1.33 (d, J = 6.4, 3H, 3-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (1-CH***C***=O), 145.1 (NH***C***=O), 135.0 (***C***-1''), 133.9 (***C***-4''), 133.8 (***C***-1'), 130.0 (***C***-Ar), 128.8 (***C***-Ar), 128.7 (***C***-Ar), 128.6 (***C***-Ar), 128.1 (***C***-Ar), 80.6 (Boc-***C***$(CH_3)_3$), 78.8 (C-2), 68.0 (CH2), 57.9 (***C***-1), 28.4 (Boc-C(***C***H_3)$_3$), 21.8 (4''-C***C***H_3), 18.3 (***C***-3); ASAP (ES) *m*/*z* 464 $[M]^+$.

_N_-Boc-L-_allo_threonine benzyl ester (307)

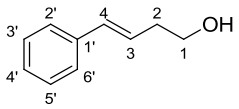


In air, Na_2CO_3 (159 mg, 1.5 mmol) was added to a solution of N-Boc-L-*allo*threonine (**306**) (110 mg, 0.5 mmol) in DMF (2.0 mL). The mixture was ice-cooled, benzyl bromide (171 mg, 1.0 mmol) added dropwise and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was filtered through celite, diluted with water, extract with ether, washed with water then brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (12g column, 0-50% EtOAc/petrol, 28 CV) afforded N-Boc-L-threonine benzyl ester (**307**) as colourless liquid (111 mg, 72%); $[\alpha]_D^{23}$ = +20 ± 1 (c = 0.5, MeOH); ν_{max} 3368, 2974, 2368, 2328, 1740, 1694, 1510, 1338, 1244, 1163, 1128, 992, 880, 742, 702, 608 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.40 (m, 5H, Ar-C***H***), 5.50 (d, *J* = 6.0, 1H, N***H***), 5.16-5.23 (m, 2H, CH_2), 4.39-4.41 (m, 1H, 1-C***H***), 4.14-4.16 (m, 1H, 2-C***H***), 3.12-3.14 (m, 1H, O***H***), 1.43 (s, 9H, Boc-C(CH_3)$_3$), 1.14 (d, *J* = 6.4, 3H, 3-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (1-CH***C***=O), 156.2 (NH***C***=O), 135.1 (***C***-1'),

128.6 (***C***-Ar), 128.5 (***C***-Ar), 128.3 (***C***-Ar), 80.5 (Boc-***C***$(CH_3)_3$), 69.0 (***C***-2), 67.3 (***C***-H_2), 59.2 (***C***-1), 28.3 (Boc-C(***C***$H_3)_3$), 18.7 (***C***-3); GC-MS (EI) *m/z* 209 $[M\text{-Boc}]^+$, 91 $[C_6H_2CH_2]^+$.

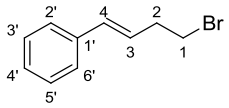
Cyclopropyl Experiments

(E)-4-Phenylbut-3-en-1-ol (310)[20]



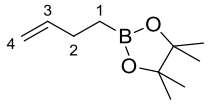
The following procedure was taken from a patent.[20] A 1 L three-necked round bottom flask equipped with a dropping funnel was flame dried, cooled under nitrogen and charged with $LiAlH_4$ (1.4 g, 37.0 mmol). To this was added THF (125 mL), and the resultant suspension was cooled using an ice bath. A solution of (E)-4-phenylbut-3-enoic acid (**309**) (5.0 g, 30.8 mmol) in THF (374 mL) was added dropwise through the pressure-equalising dropping funnel and the reaction mixture was allowed to warm to room temperature and stirred for another 1.5 h. The reaction mixture was slowly quenched with aq. NaOH (1.0 M, 1.8 L), diluted with water (150 mL), extracted into ethyl acetate, dried over MgSO4 and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (80 g column, 0-50% EtOAc/hexane, 9 column volumes) afforded (E)-4-phenylbut-3-en-1-ol (**310**) as colourless liquid (3.83 g, 84%); ν_{max} 3270, 2934, 2848, 1956, 1498, 1447, 1332, 1175, 1037, 960, 738, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, 2H, *J* = 7.6, 2',6'-C***H***), 7.31 (t, *J* = 7.6, 2H, 3',5'-C***H***), 7.18-7.24 (m, 1H, 4'-C***H***), 6.50 (d, *J* = 15.6, 1H, 4-C***H***), 6.18-6.25 (m, 1H, 3-C***H***), 3.76 (t, *J* = 6.4, 2H, 1-CH_2), 4.92 (q, *J* = 6, 2H, 2-CH_2), 1.73 (sbr, 1H, O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4 (***C***-1'), 132.9 (***C***-4), 128.7 (***C***-3',5'), 127.4 (***C***-4'), 126.5 (***C***-2',6'), 126.2 (***C***-3), 62.1 (***C***-1), 36.5 (***C***-2); GC-MS (EI) *m/z* 148 $[M]^+$, 117 $[M\text{-}CH_2OH]^+$, 91 $[M\text{-}(CH_2)_3OH]^+$; HRMS (ASAP) *m/z* calculated $[M+H]^+$ 149.0961, found $[M]^+$ 149.0962.

(E)-(4-Bromobut-1-en-1-yl)benzene (311)[21]



Under N_2, a solution of PBr_3 (1.6 g, 6.0 mmol) in benzene (12 mL) was added dropwise to ice-cooled solution of (E)-4-phenylbut-3-en-1-ol (**310**) (1.8 g, 12.0 mmol) in benzene (12 mL). The reaction mixture was refluxed for 3 h, cooled to 0 ˚C and quenched with ice. The mixture was extracted into benzene, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (80 g column, 0-10% DCM/hexane, 9 column volumes) afforded (E)-(4-bromobut-1-en-1-yl)benzene (**311**) as colourless liquid (55%); ν_{max} 3026, 2938, 1498, 1454, 1254, 1207, 960, 742, 688, 645, 561 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, 2H, *J* = 7.2, 2',6'-C***H***), 7.23-7.26 (m, 2H, 3',5'-C***H***), 7.15-7.18 (m, 1H, 4'-C***H***), 6.420 (d, *J* = 16.0, 1H, 4-C***H***), 6.12 (td, 1H, J = 16.0 and 6.8, 3-C***H***), 3.41 (t, *J* = 6.8, 2H, 1-C$\mathbf{H_2}$), 4.92 (dq, *J* = 6.8, ^4J = 1.2, 2H, 2-C$\mathbf{H_2}$), 1.73 (sbr, 1H, O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (***C***-1'), 132.8 (***C***-4), 128.7 (***C***-3',5'), 127.6 (***C***-4'), 126.8 (***C***-2',6'), 126.3 (***C***-3), 36.4 (***C***-2), 32.3 (***C***-1); GC-MS (EI) *m/z* 212 ($[M]^+$, ^{81}Br), 210 ($[M]^+$, ^{79}Br), 131 $[M-Br]^+$, 117 $[M-CH_2Br]^+$, 91 $[M-(CH_2)_3Br]^+$; HRMS (ASAP) *m/z* calculated $[M]^+$ 210.0039, found $[M]^+$ 210.0041.

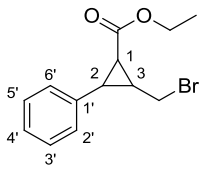
2-(But-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (314)



General Procedure L was applied to (bromomethyl)cyclopropane (**313**) (135 mg, 1.0 mmol) with PPh_3 replaced with polymer-supported PPh_3 (13 mol%). Purification by flash column

chromatography (24 g column, 0-100% DCM/hexane, 26 column volumes) afforded 2-(but-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**314**) as colourless liquid (149 mg, 82%). Similar yield (155 mg, 85%) was obtained from the borylation of 4-bromo-but-1-ene (**317**) (135 mg, 1.0 mmol) under identical conditions; ν_{max} 2977, 2928, 1742, 1369, 1324, 1245, 1214, 1146, 967, 845, 676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83-5.93 (m, 1H, 3-C***H***), 4.87-5.02 (m, 2H, 4-C***H***$_2$), 2.14-2.19 (m, 2H, 2-C***H***$_2$), 1.24 (s, 12H, pin-CC***H***$_3$), 0.88 (t, *J* = 7.6, 2H, 1-C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (***C***-3), 113.3 (***C***-4), 83.1 (pin-***C***CH_3), 28.1 (***C***-2), 25.0 (pin-C***C***H_3); ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0; GC-MS (EI) *m/z* 182 $[M]^+$, 167 $[M\text{-}CH_3]^+$, 153 $[M\text{-}CH_2CH_3]^+$, 125 $[M\text{-}CH_2CHCH_2CH_2]^+$, 96, 83, 55; HRMS (ASAP) *m/z* calculated $[M]^+$ 182.1426, found $[M]^+$ 182.1429.

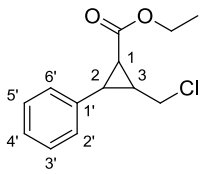
Ethyl 2-(bromomethyl)-3-phenylcyclopropanecarboxylate (318)



Under N_2, ethyl diazoacetate (0.34 g, 3.0 mmol) in cyclohexane (5.0 mL) was added over 24 h to a stirred mixture of $Rh_2(OAc)_4$ (13 mg, 1 mol%) and (E)-(4-bromobut-1-en-1-yl)benzene (**305**) (1.90 g, 9.0 mmol) at room temperature. The reaction mixture was diluted with ether, washed with aq. HCl (10% wt.), dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (40 g column, 0-10% EtOAc/hexane, 24 column volumes) afforded ethyl 2-(bromomethyl)-3-phenylcyclopropanecarboxylate (**318**) as colourless liquid (68 mg, 8%); ν_{max} 2978, 1719, 1378, 1222, 1196, 1156, 1030, 750, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.32 (m, 2H,

3',5'-C***H***), 7.21-7.25 (m, 1H, 4'-C***H***), 7.12 (d, *J* = 7.2, 2H, 2',6'-C***H***), 4.18-4.27 (m, 2H, OC***H***$_2$CH$_3$), 3.73-3.93 (m, 2H, C***H***$_2$Br), 2.67-2.72 (m, 1H, 2-C***H***), 2.26-2.30 (m, 1H, 3-C***H***), 2.13-2.21 (m, 1H, 1-C***H***), 1.32 (t, *J* = 7.2, 3H, OCH$_2$C***H***$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.8 (***C***=O), 138.6 (***C***-1'), 128.8 (***C***-3',5'), 127.1 (***C***-4'), 126.5 (***C***-2',6'), 61.2 (O***C***H$_2$CH$_3$), 34.2 (***C***-2), 32.6 (***C***H$_2$Br), 30.9 (***C***-3), 30.3 (***C***-1), 14.4 (OCH$_2$***C***H$_3$); GC-MS (EI) *m/z* 284 ([M]$^+$, ^{81}Br), 282 ([M]$^+$, ^{79}Br), 239 ([M-OCH$_2$CH$_3$]$^+$, ^{81}Br), 237 ([M-OCH$_2$CH$_3$]$^+$, ^{79}Br), 203 [M-Br]$^+$; HRMS (ASAP) *m/z* calculated [M]$^+$ 282.0250, found [M]$^+$ 282.0255.

Ethyl 2-(chloromethyl)-3-phenylcyclopropanecarboxylate (319)



Under N$_2$, ethyl diazoacetate (0.34 g, 3.0 mmol) in cyclohexane (5.0 mL) was added over 24 h to a stirred mixture of Rh$_2$(OAc)$_4$ (13 mg, 1 mol%) and (E)-(4-chlorobut-1-en-1-yl)benzene (1.50 g, 9.0 mmol) at room temperature. The reaction mixture was diluted with ether, washed with aq. HCl (10% wt.), dried over MgSO$_4$ and concentrated under reduced pressure to give a crude mixture. Purification by flash column chromatography (40 g column, 0-20 % EtOAc/hexane, 24 column volumes) afforded ethyl 2-(chloromethyl)-3-phenylcyclopropanecarboxylate (**319**) as colourless liquid (0.23 g, 32%); ν_{max} 2978, 1716, 1432, 1378, 1199, 1160, 1023, 853, 746, 698 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.28-7.32 (m, 2H, 3',5'-C***H***), 7.21-7.24 (m, 1H, 4'-C***H***), 7.11 (d, *J* = 8.4, 2H, 2',6'-C***H***), 4.17-4.26 (m, 2H, OC***H***$_2$CH$_3$), 3.85-4.06 (m, 2H, C***H***$_2$Cl), 2.67-2.70 (m, 1H, 2-C***H***), 2.21-2.25 (m, 1H, 3-C***H***), 2.07-2.15 (m, 1H, 1-C***H***), 1.31 (t, *J* = 6.8, 3H, OCH$_2$C***H***$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.0 (***C***=O),

138.7 (***C***-1'), 128.8 (***C***-3',5'), 127.1 (***C***-4'), 126.5 (***C***-2',6'), 61.2 (O***C***H_2CH_3), 42.6 (***C***-2), 32.6 (***C***H_2Cl), 32.2 (***C***-3), 29.0 (***C***-1), 14.4 (OCH_2***C***H_3); GC-MS (EI) *m/z* 240 ($[M]^+$, ^{37}Cl), 238 ($[M]^+$, ^{35}Cl), 191 $[M\text{-}CH_2Cl]^+$; HRMS (ASAP) *m/z* calculated $[M]^+$ 238.0755, found $[M]^+$ 238.0760.

6.4 References

[1] Gardner, J. H.; Naylor, C. A. *Org. Synth.* **1936**, *16*, 71.

[2] Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574.

[3] Vitullo, V. P.; Sridharan, S.; Johnson, L. P. *J. Am. Chem. Soc.* **1979**, *101*, 2320.

[4] Adger, B. M.; Bannister, R.; Lewis, N. J.; O'Farrell, C. *J. Chem. Soc., Perkin Trans. 1* **1988**, *0*, 2785.

[5] Schlosser, M.; Marull, M. *Eur. J. Org. Chem.* **2003**, *2003*, 1569.

[6] Krawczyk, S.; Otto, M.; Otto, A.; Coburger, C.; Krug, M.; Seifert, M.; Tell, V.; Molnár, J.; Hilgeroth, A. *Bioorg. Med. Chem.* **2011**, *19*, 6309.

[7] Dirania, M. K. M.; Hill, J. *Journal of the Chemical Society C-Organic* **1971**, 1213.

[8] Zhang, T.; Shi, M. *Chem. Eur. J.* **2008**, *14*, 3759.

[9] Tamaru, Y.; Yamada, Y.; Arimoto, T.; Yoshida, Z. *Chem. Lett.* **1978**, 975.

[10] Cho, J. Y.; Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 12868.

[11] Lata, C. J.; Crudden, C. M. *J. Am. Chem. Soc.* **2010**, *132*, 131.

[12] Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.

[13] Pintaric, C.; Olivero, S.; Gimbert, Y.; Chavant, P. Y.; Dunach, E. *J. Am. Chem. Soc.* **2010**, *132*, 11825.

[14] Karatjas, A. G.; Vedejs, E. *J. Org. Chem.* **2008**, *73*, 9508.

[15] Guennouni, N.; Lhermitte, F.; Cochard, S.; Carboni, B. *Tetrahedron* **1995**, *51*, 6999.

[16] Mori, K. *Eur. J. Org. Chem.* **2005**, *2005*, 2040.

[17] Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 5404.

[18] Mosher, C. W.; Goodman, L. *J. Org. Chem.* **1972**, *37*, 2928.

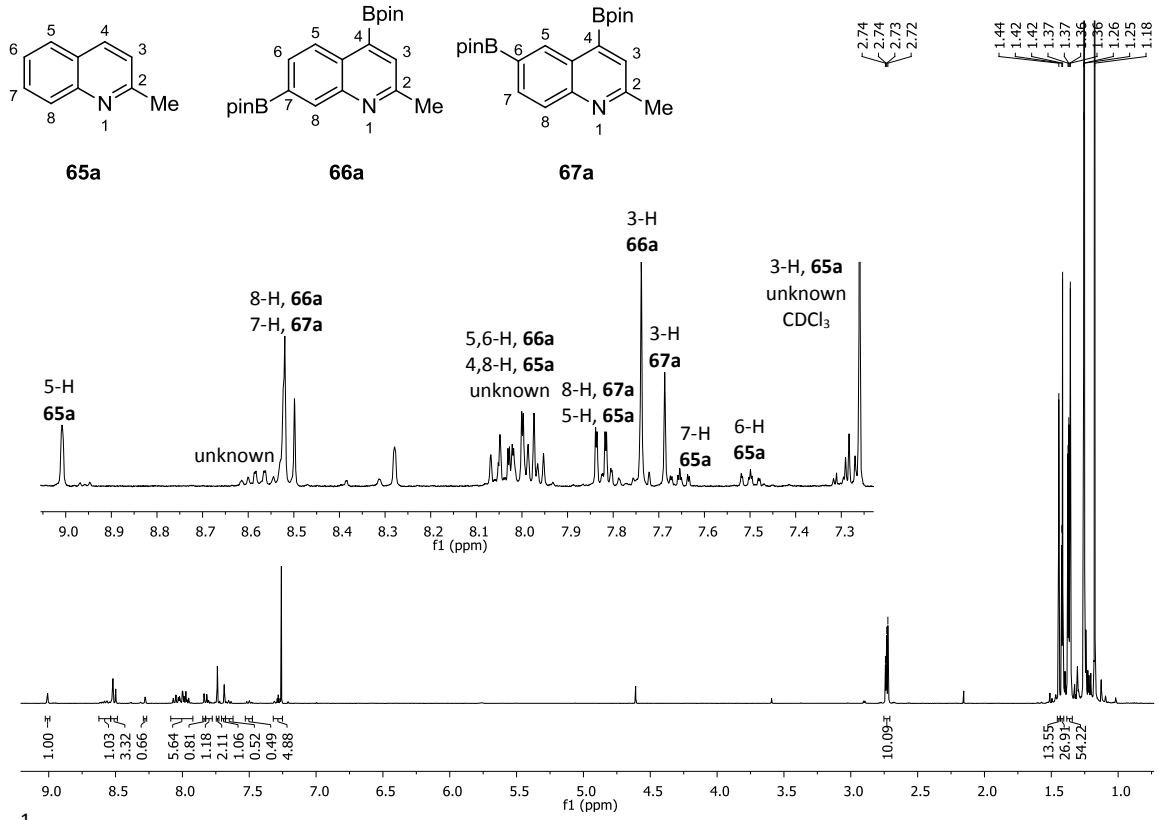
[19] Zhou, H.; van der Donk, W. A. *Org. Lett.* **2002**, *4*, 1335.

[20] Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265.

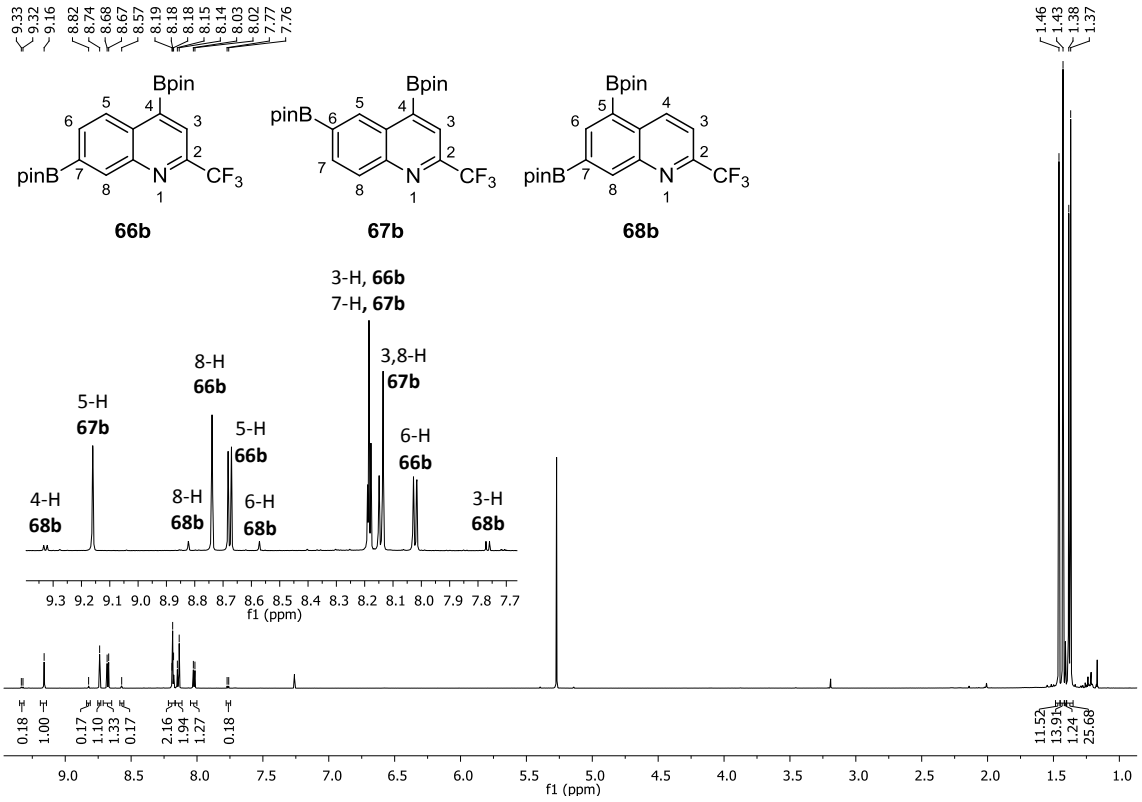
[21] Jung, M. E.; Angelica, S.; D'Amico, D. C. *J. Org. Chem.* **1997**, *62*, 9182.

Appendix - NMR Spectra

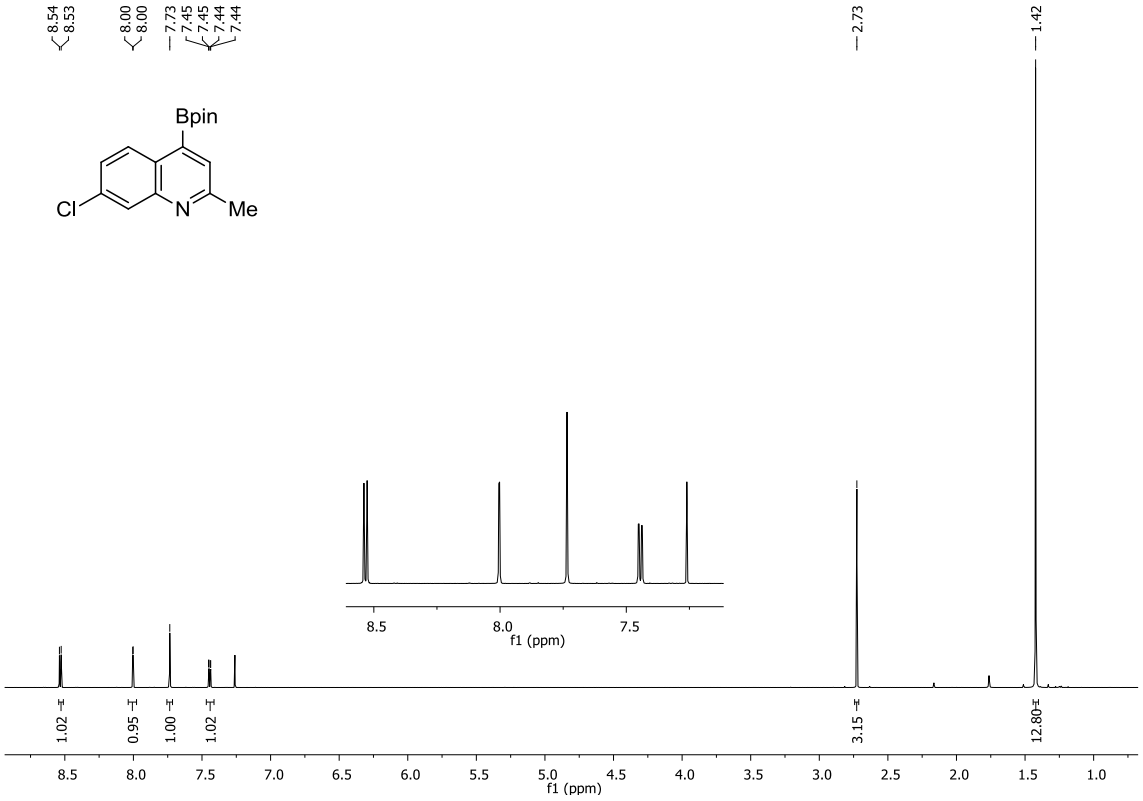
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 2-methylquinoline (**65a**)



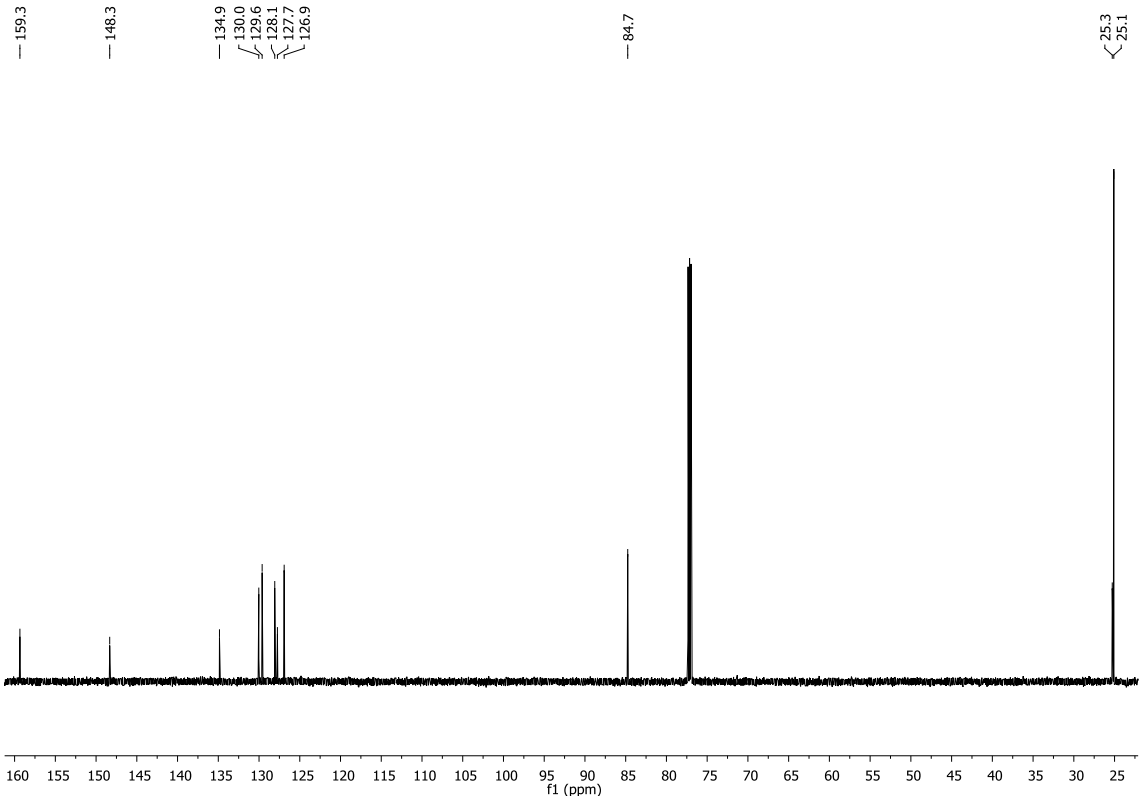
^{1}H NMR (600 MHz, $CDCl_3$) - Borylation of 2-(trifluoromethyl)quinoline (**65b**)



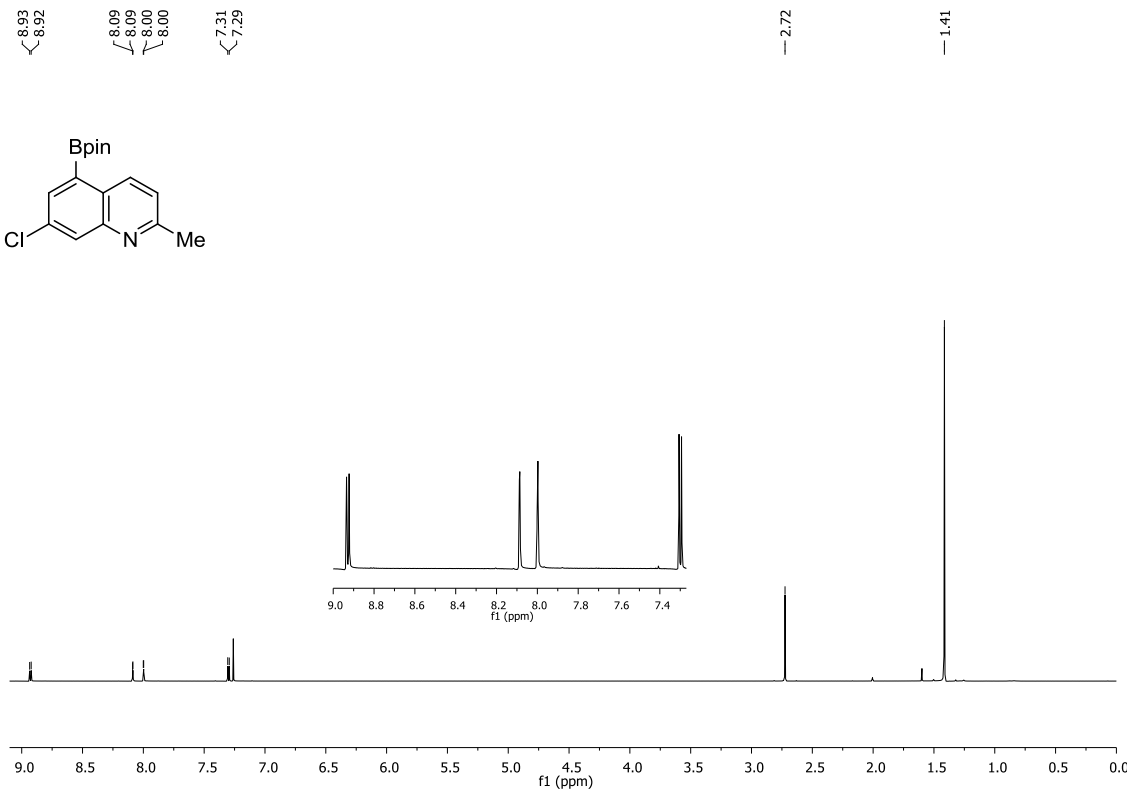
^{1}H NMR (700 MHz, $CDCl_3$) – **63f**



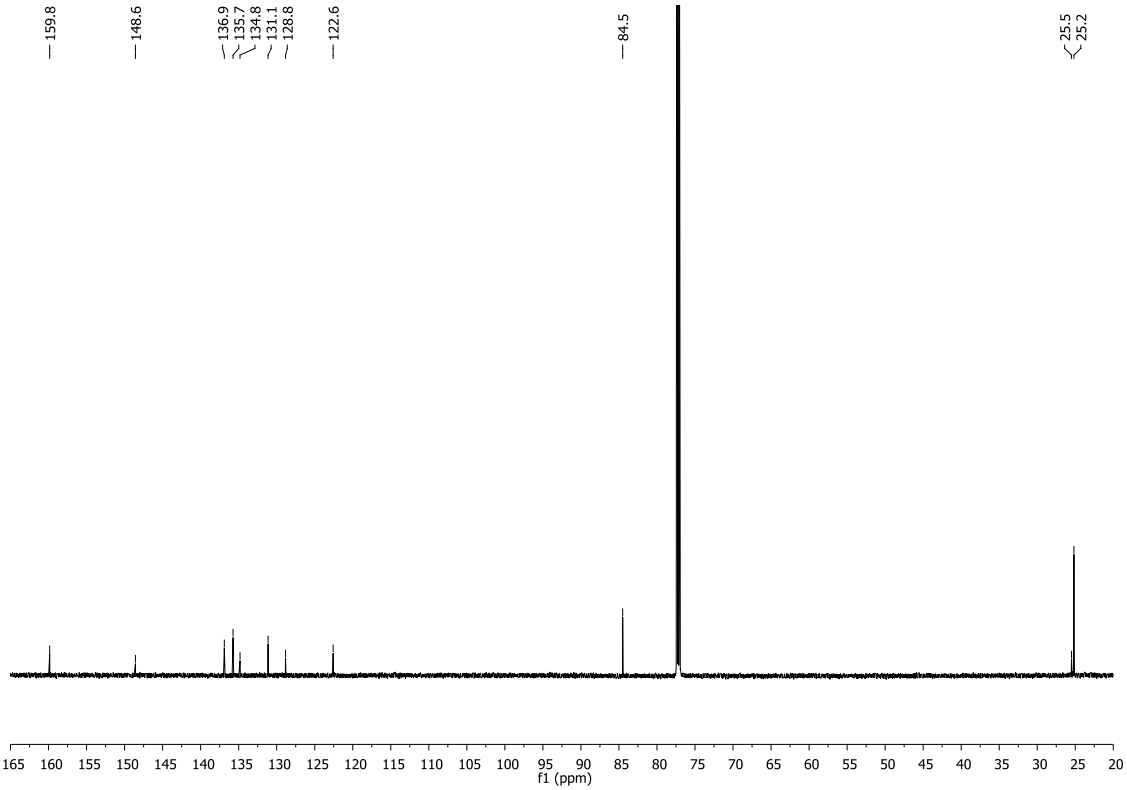
^{13}C NMR (176 MHz, $CDCl_3$) – **63f**



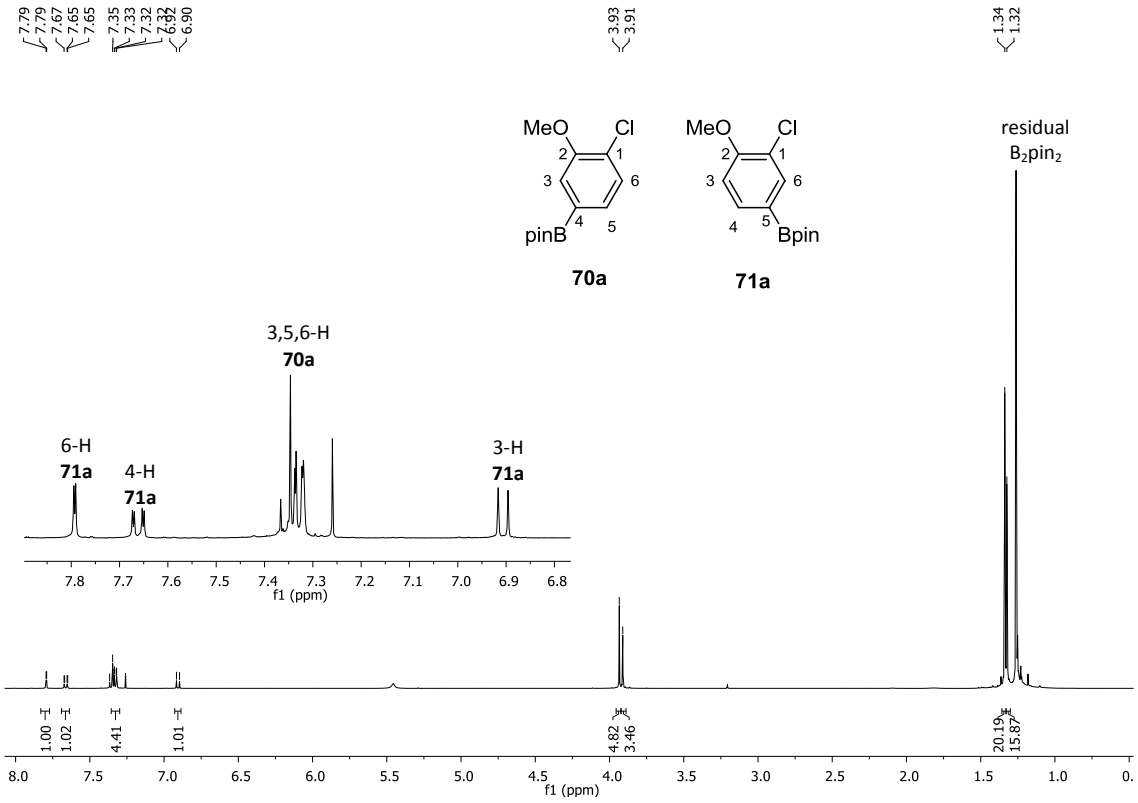
^{1}H NMR (700 MHz, $CDCl_3$) – **64f**



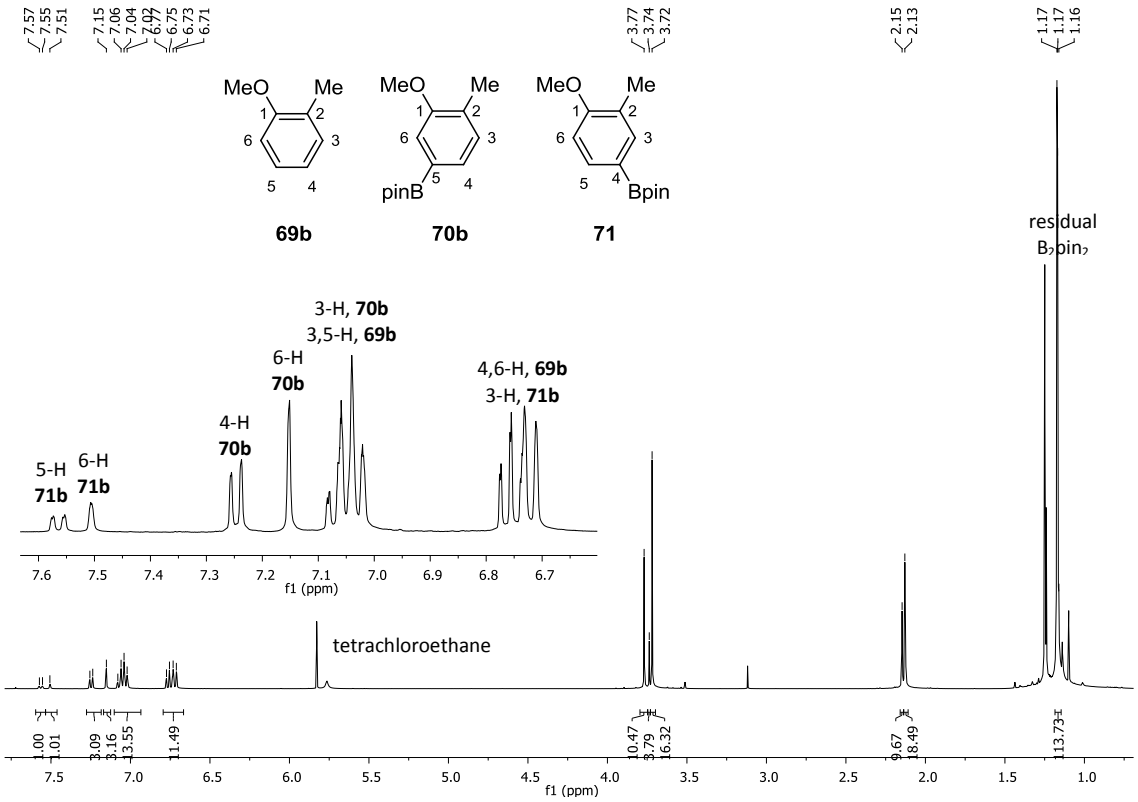
^{13}C NMR (176 MHz, $CDCl_3$) – **64f**



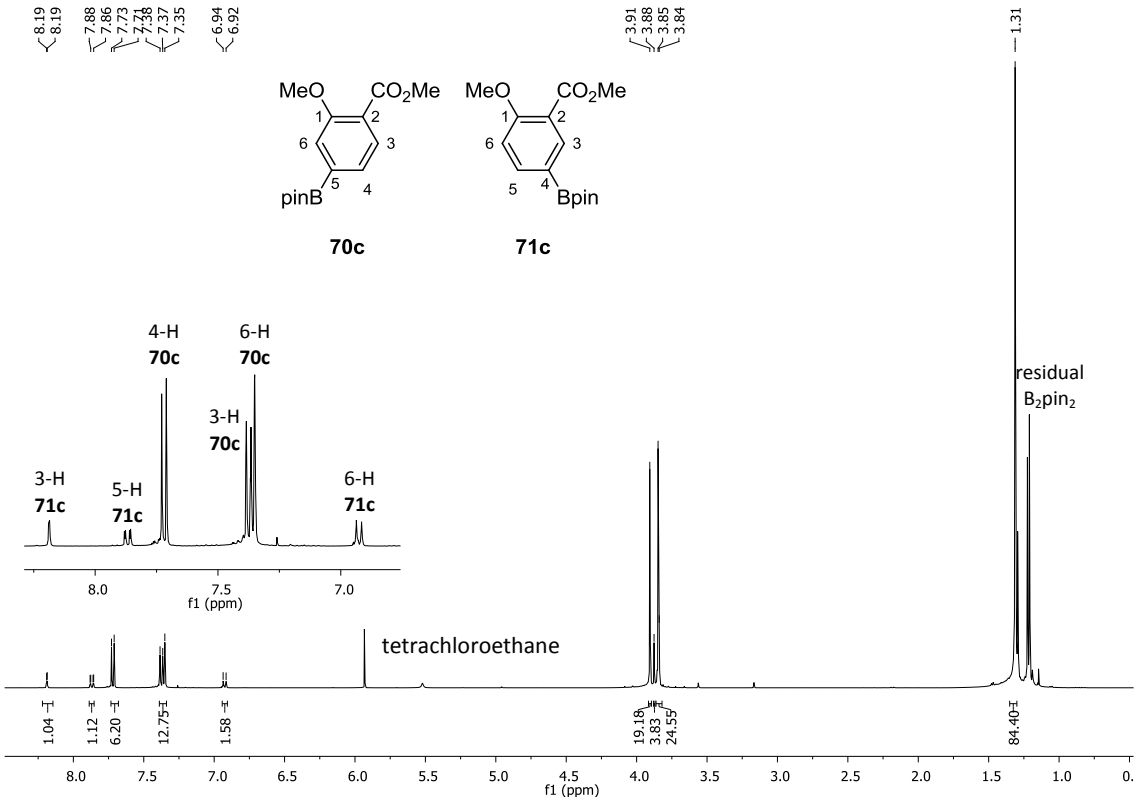
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 1-chloro-2-methoxybenzene (**69a**)



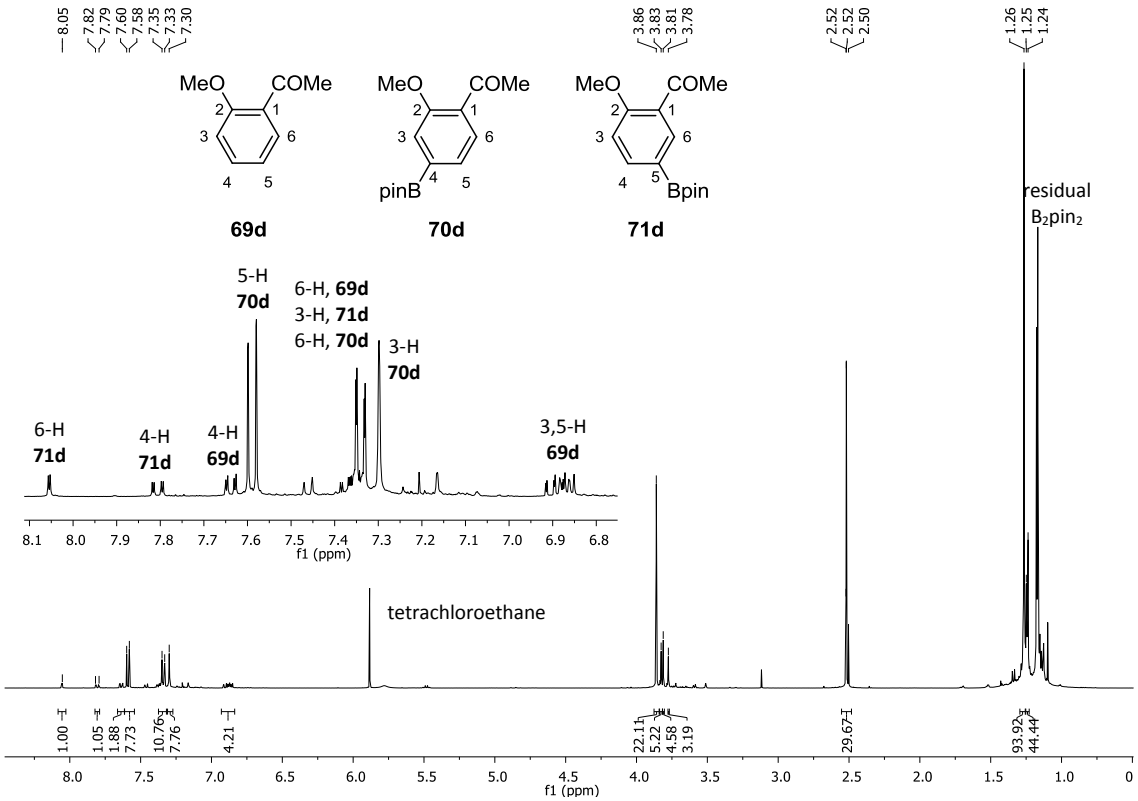
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 1-methoxy-2-methylbenzene (**69b**)



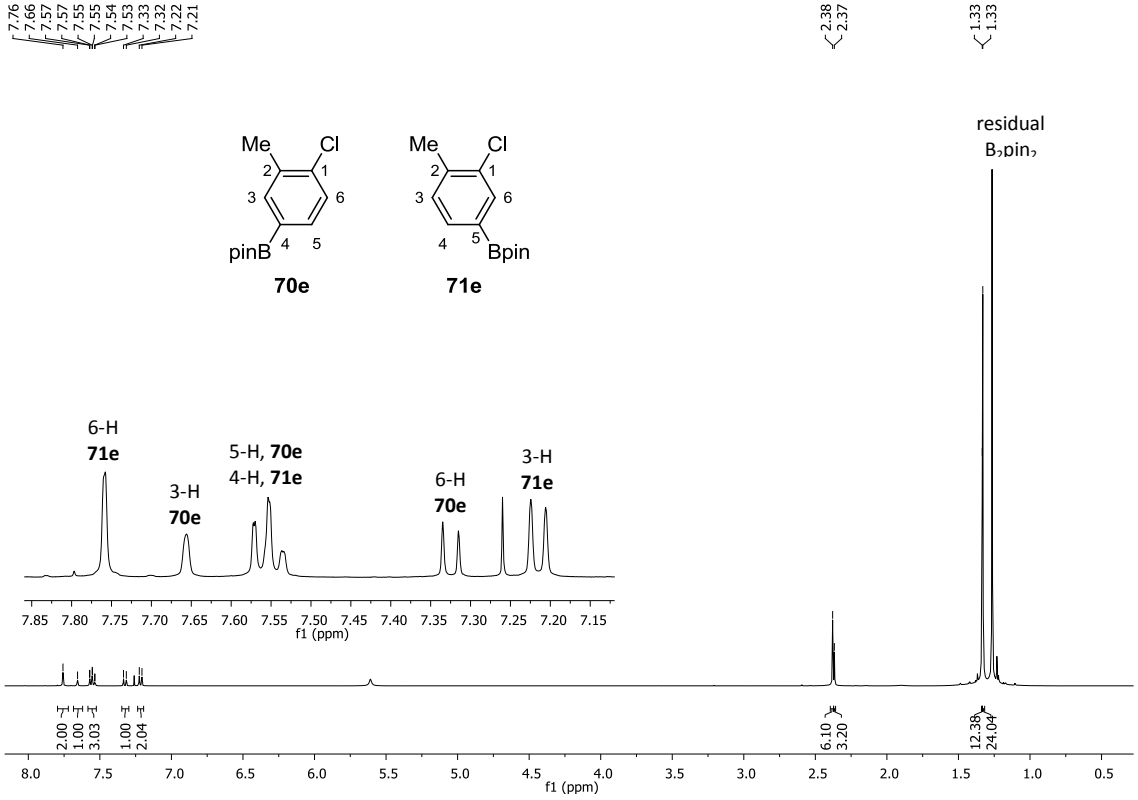
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of methyl 2-methoxybenzoate (**69c**)



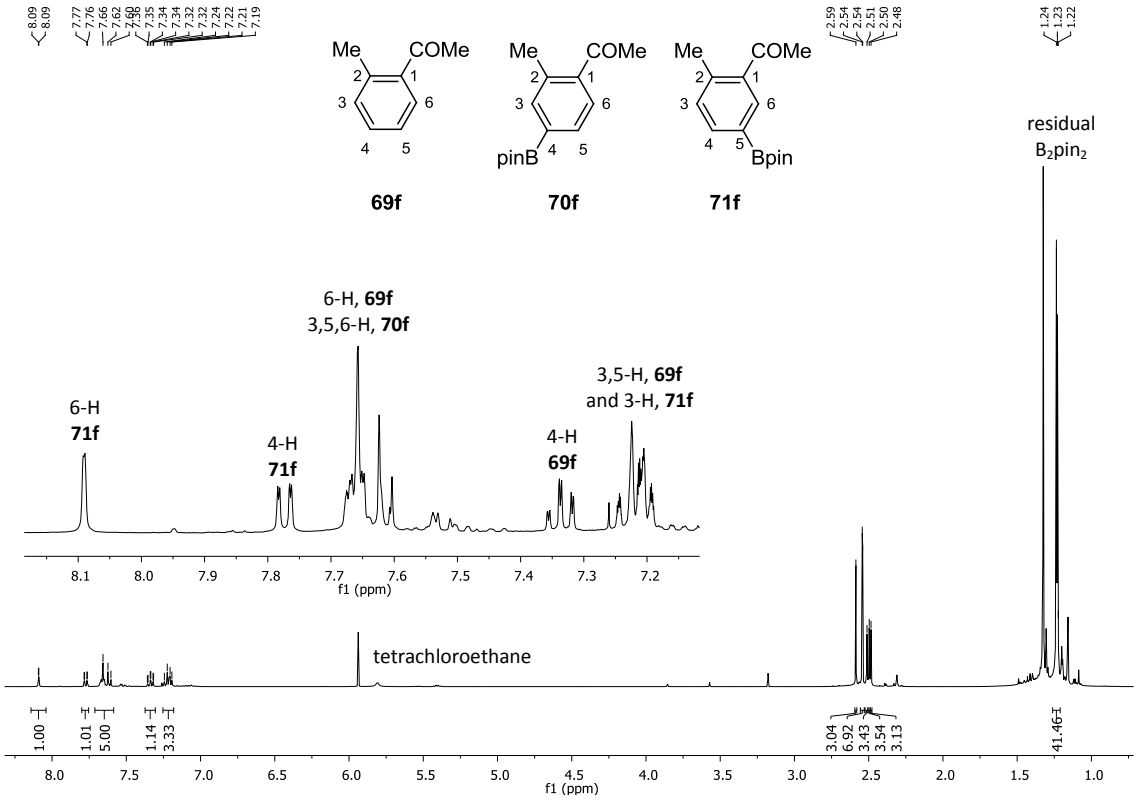
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 1-(2-methoxyphenyl)ethanone (**69d**)



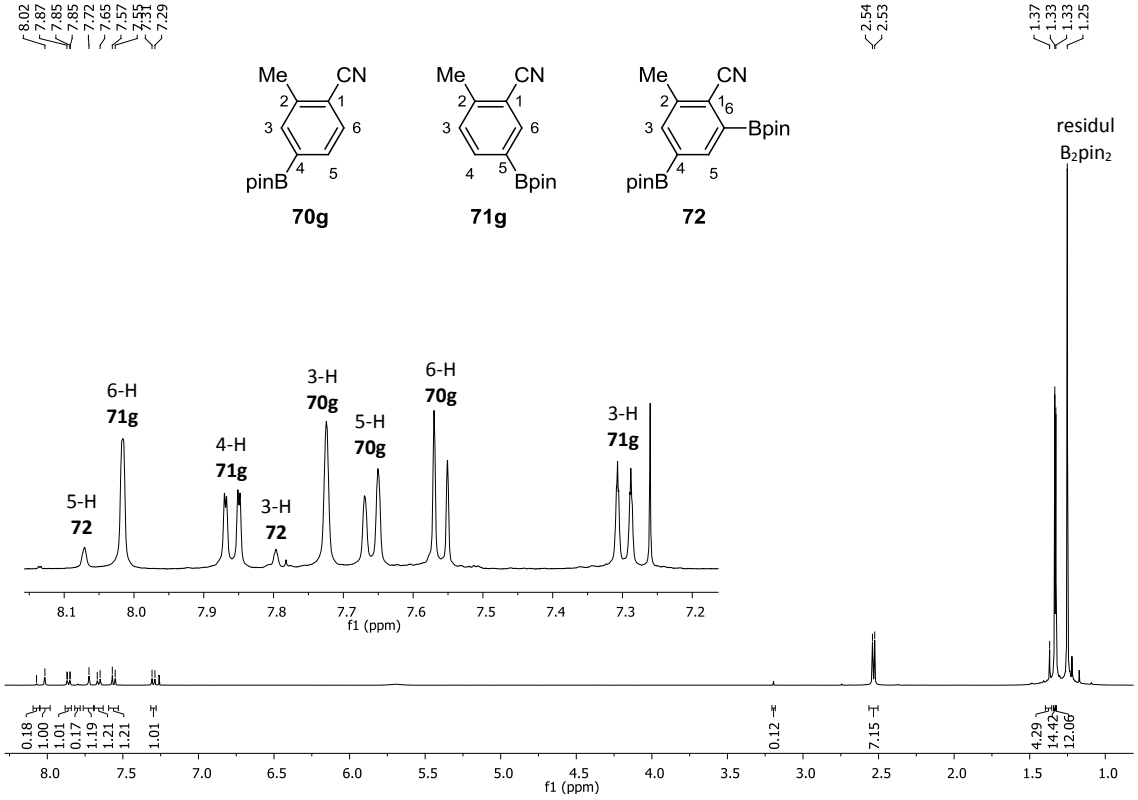
^{1}H NMR (400 MHz, $CDCl_3$) – Borylation of 1-chloro-2-methylbenzene (**69e**)



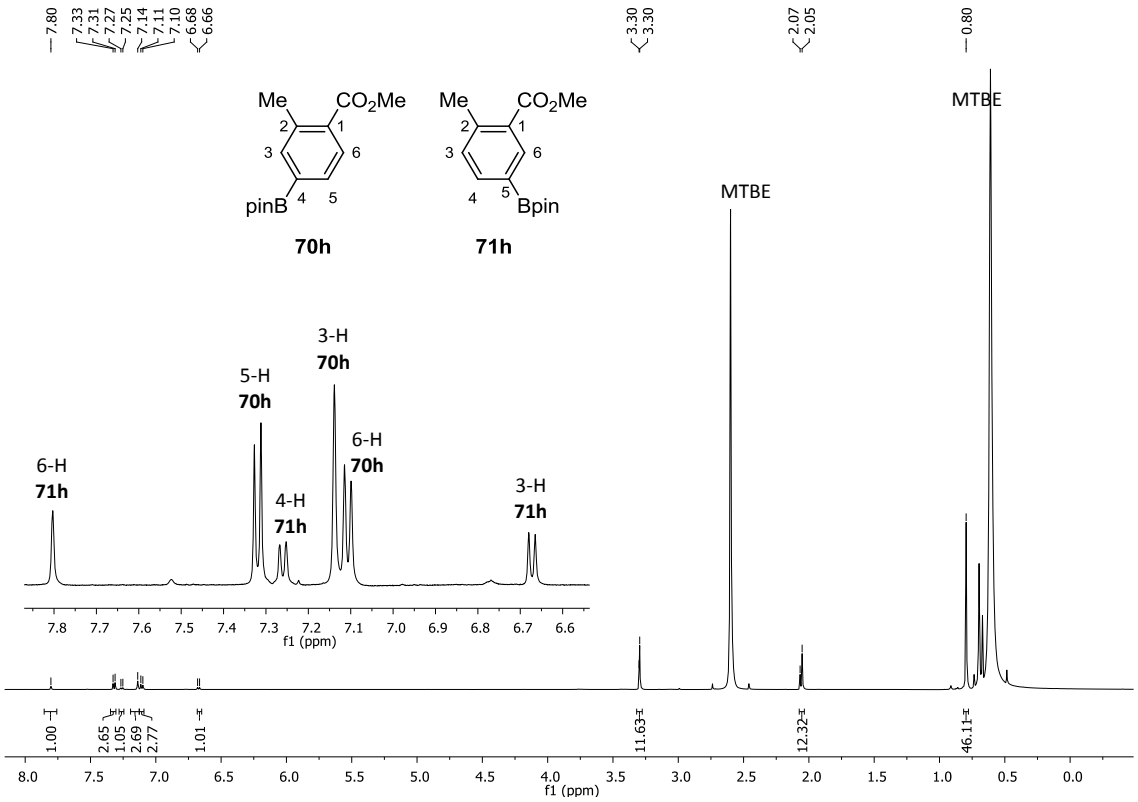
^{1}H NMR (400 MHz, $CDCl_3$) – Borylation of 1-(2-methylphenyl)ethanone (**69f**)



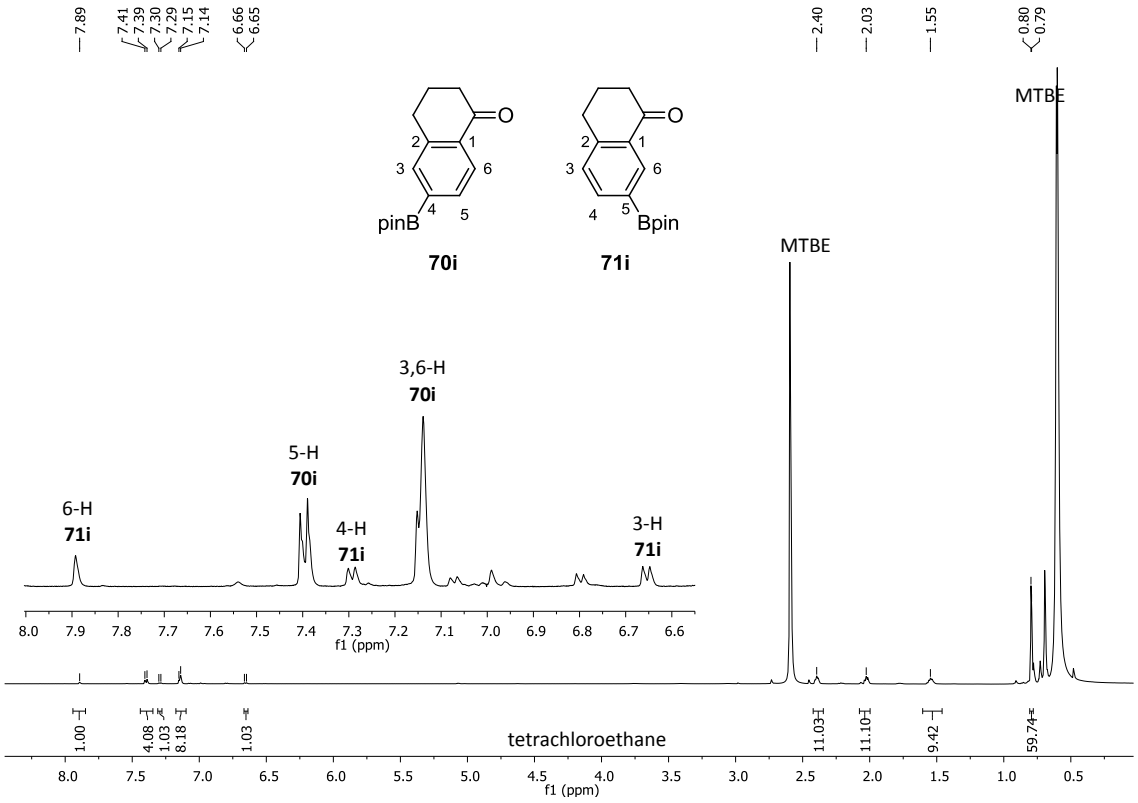
^{1}H NMR (400 MHz, $CDCl_3$) – Borylation of 2-methylbenzonitrile (**69g**)



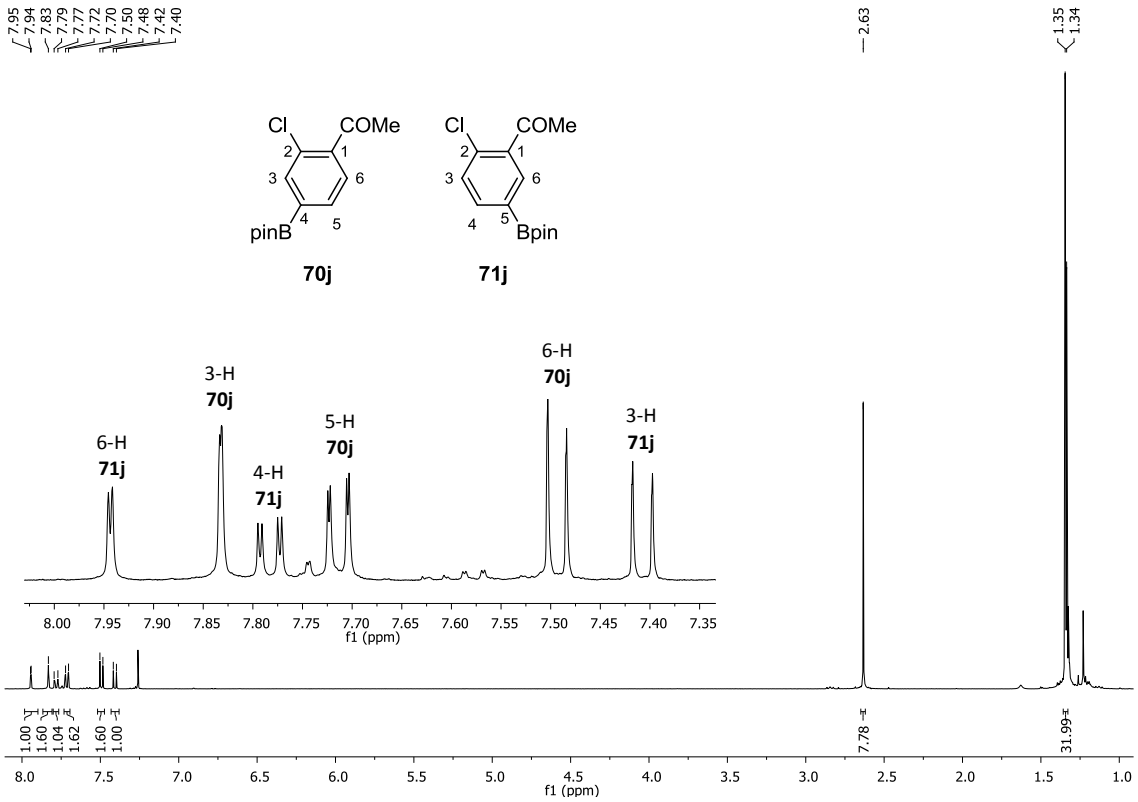
^{1}H NMR (400 MHz, acetone-d_6) – Borylation of methyl 2-methylbenzoate (**69h**)



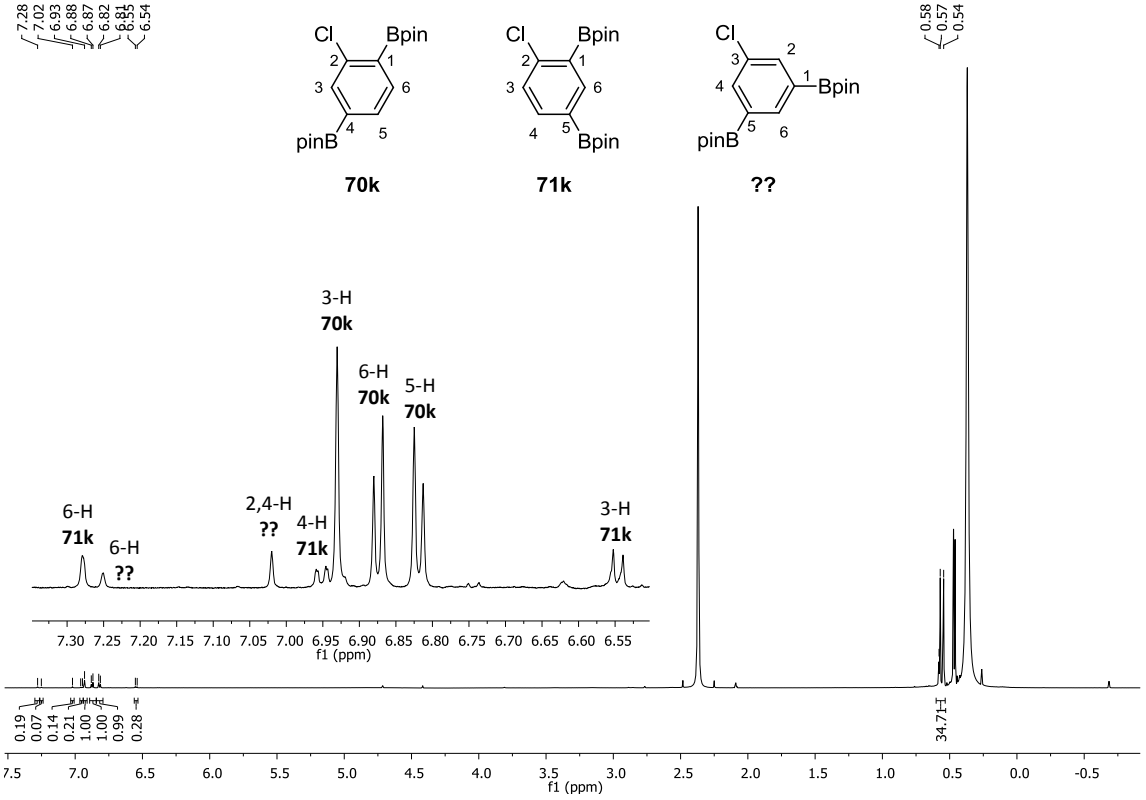
^{1}H NMR (400 MHz, acetone-d_6) - Borylation of 3,4-dihydronaphthalen-1(2*H*)-one (**69i**)



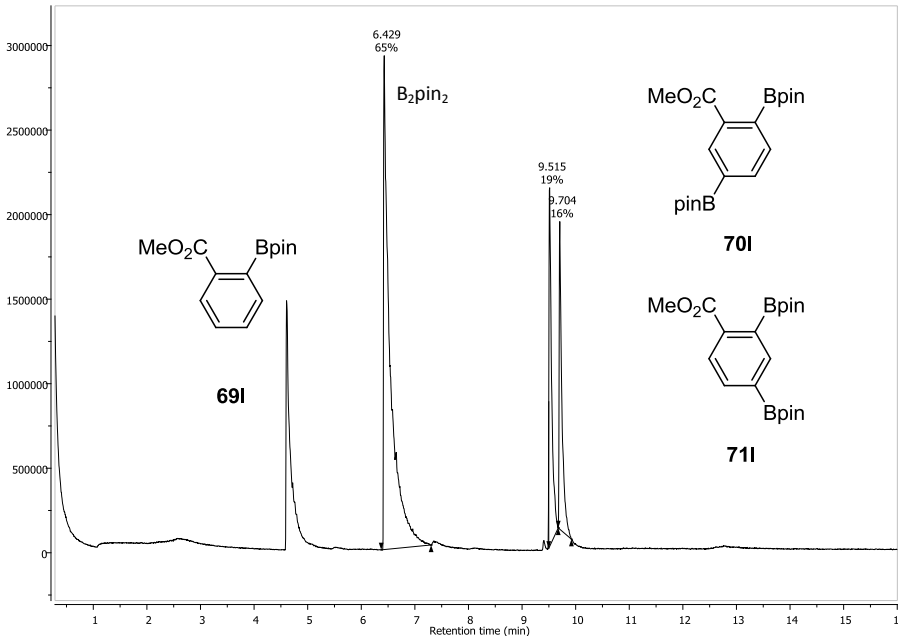
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 1-(2-chlorophenyl)ethanone (**69j**)



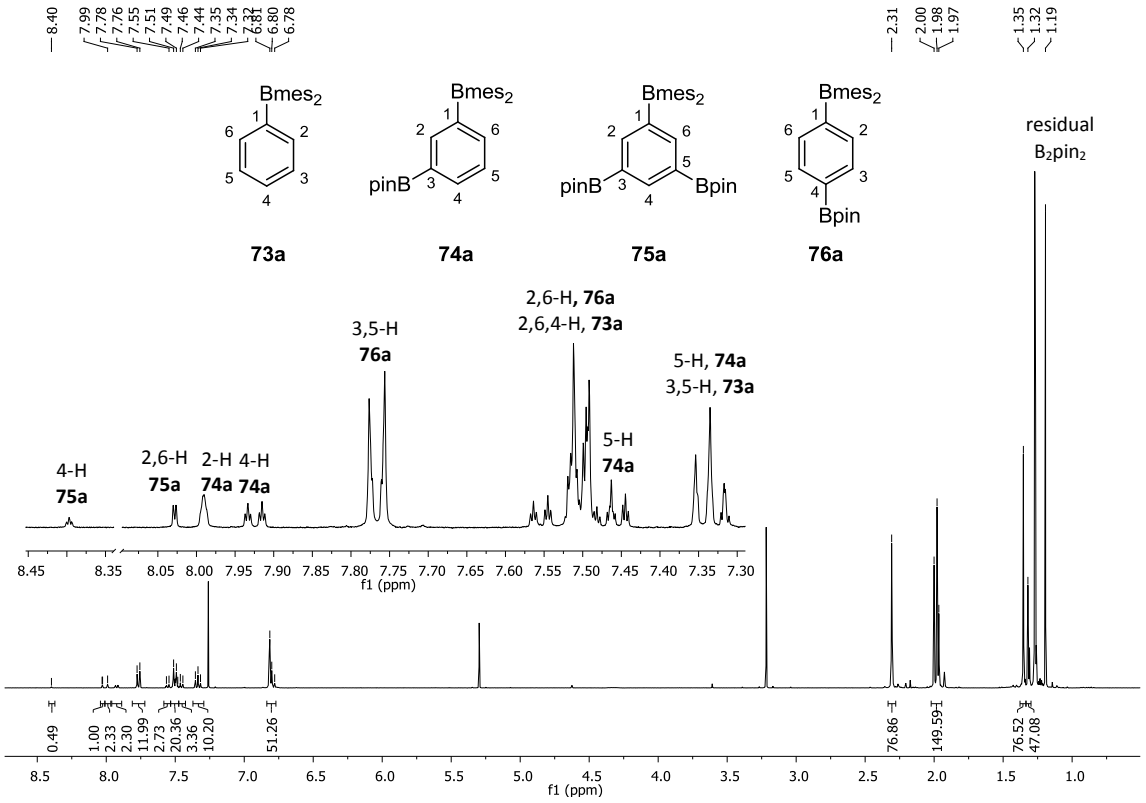
^{1}H NMR (600 MHz, acetone-d_6) - Borylation of 2-(Bpin)chlorobenzene (**69k**)



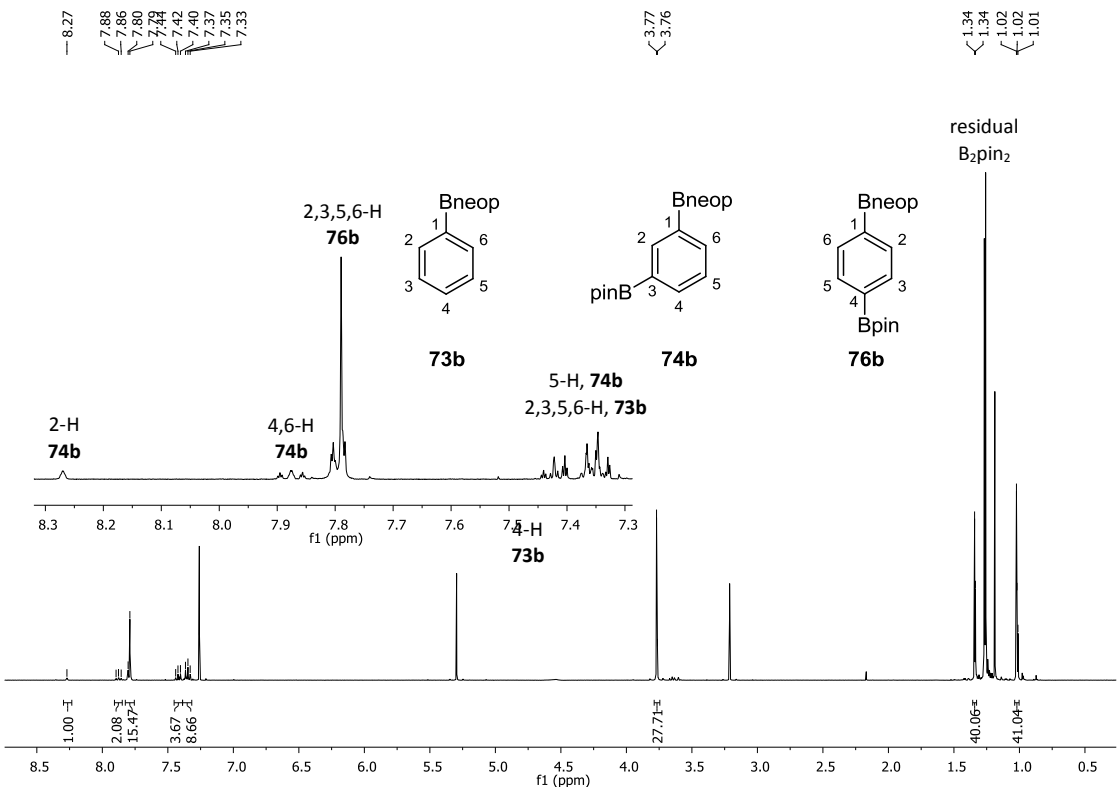
GC-MS - Borylation of methyl 2-(Bpin)benzoate (**69l**)



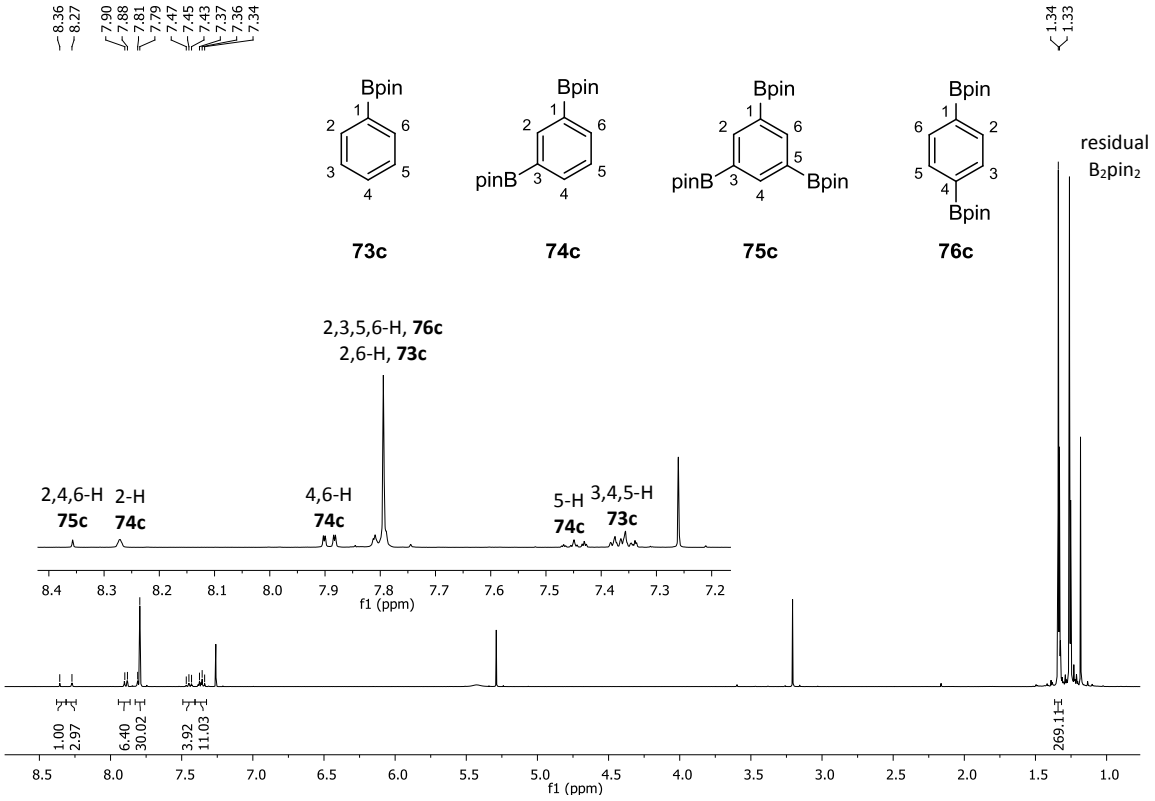
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of phenylBmes$_2$ (**73a**)



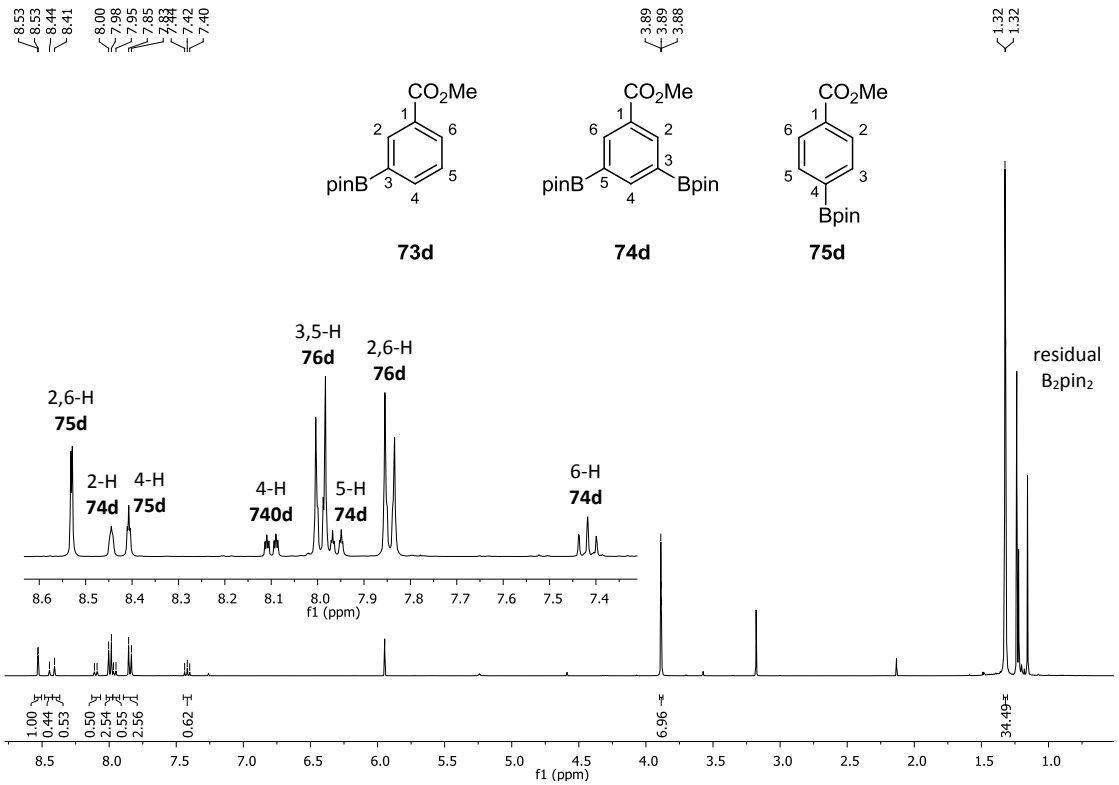
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of phenylBneop (**73b**)



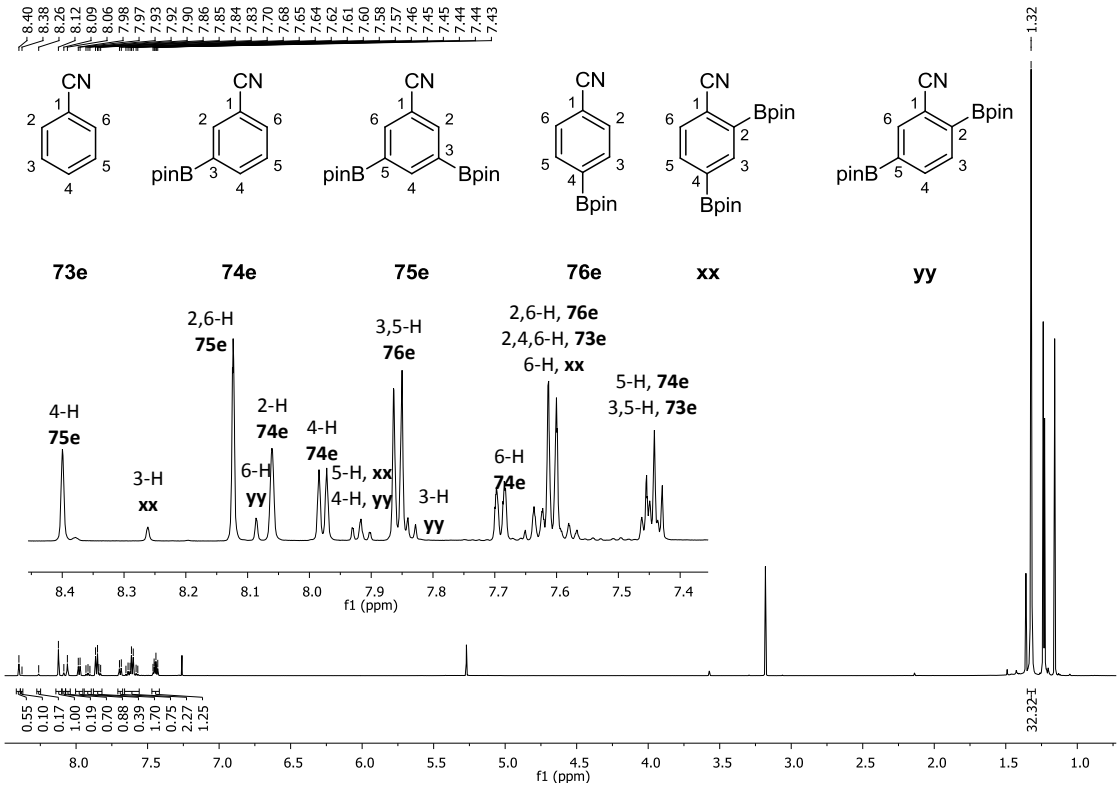
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of phenylBpin (**73c**)



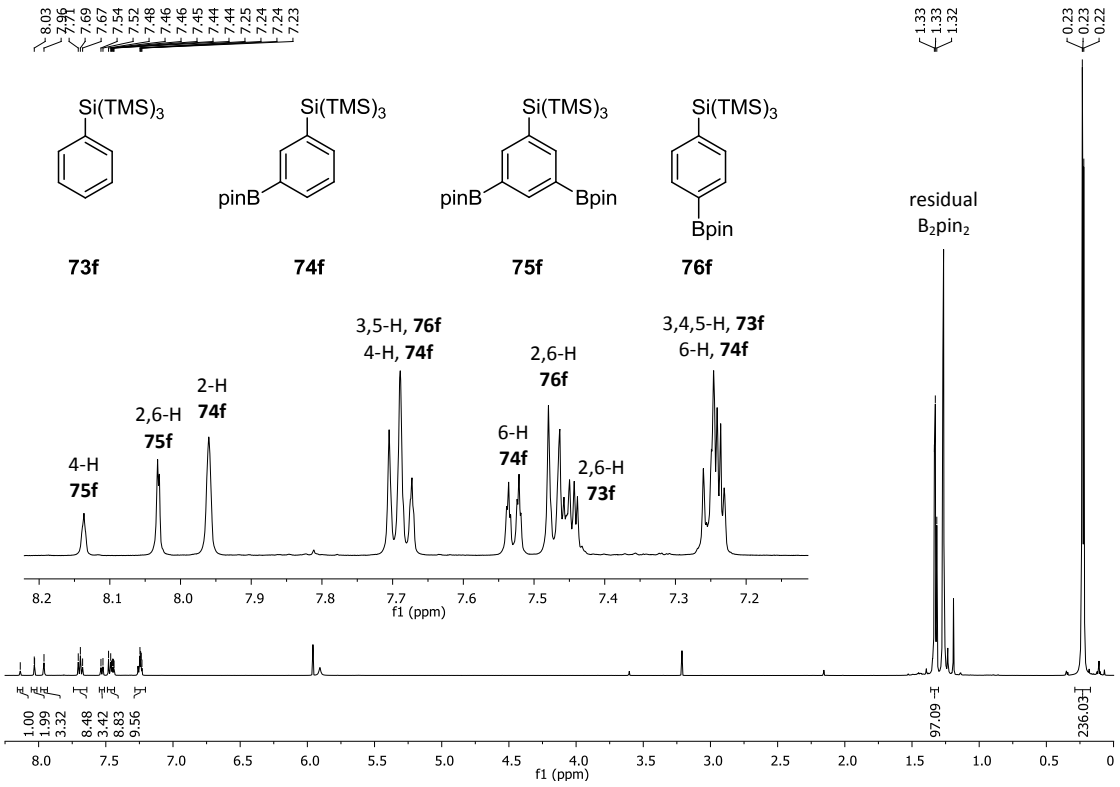
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of methyl benzoate (**73d**)



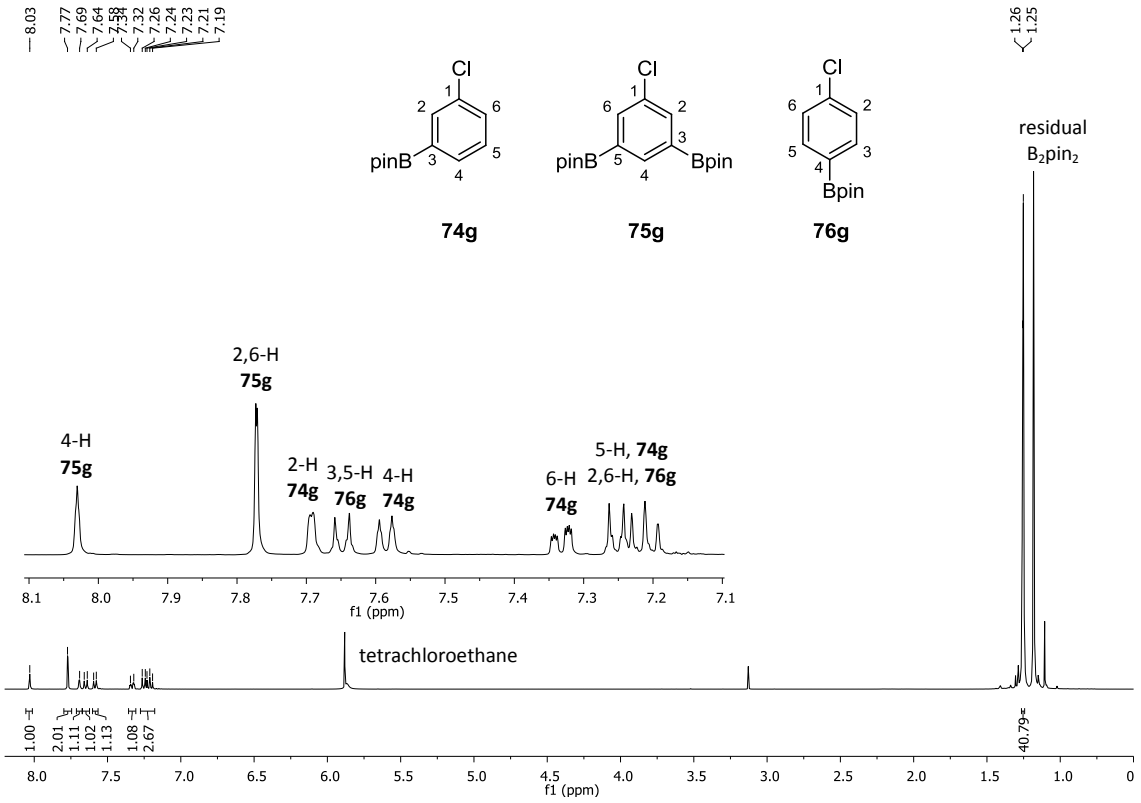
^{1}H NMR (500 MHz, $CDCl_3$) - Borylation of benzonitrile (**73e**)



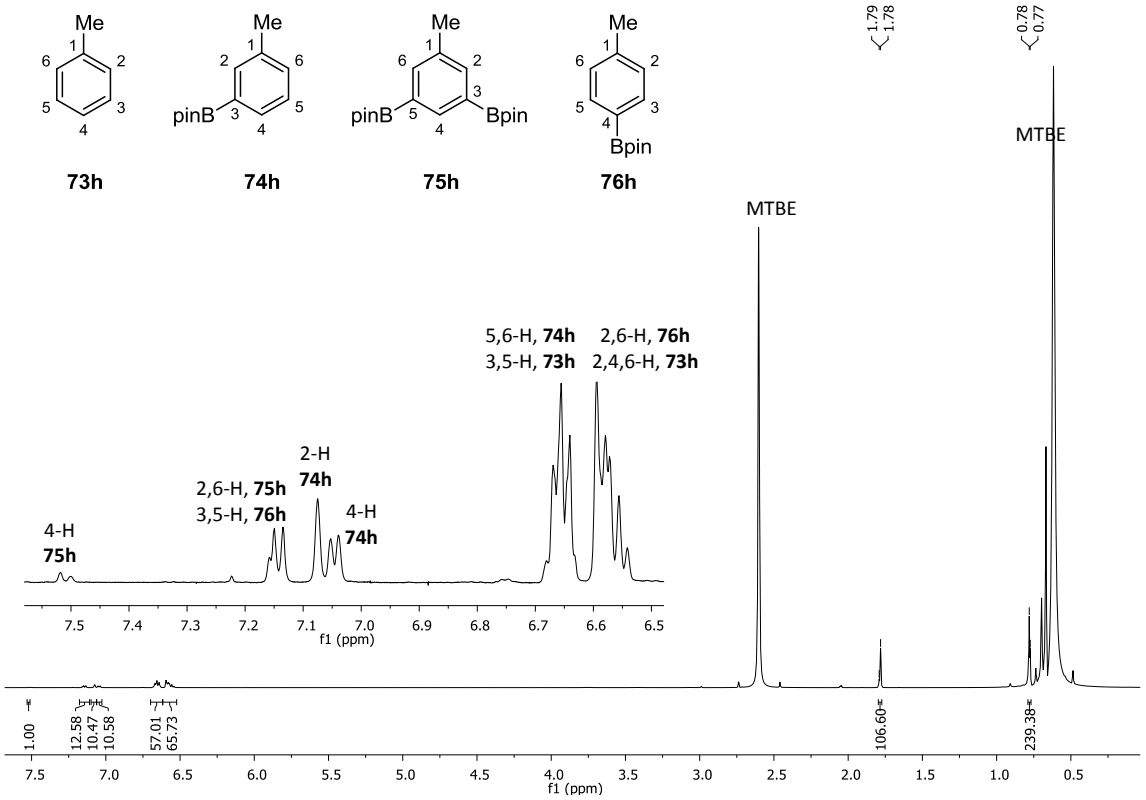
H NMR (500 MHz, $CDCl_3$) - Borylation of phenyl(trimethylsilyl)trisilane (**73f**)



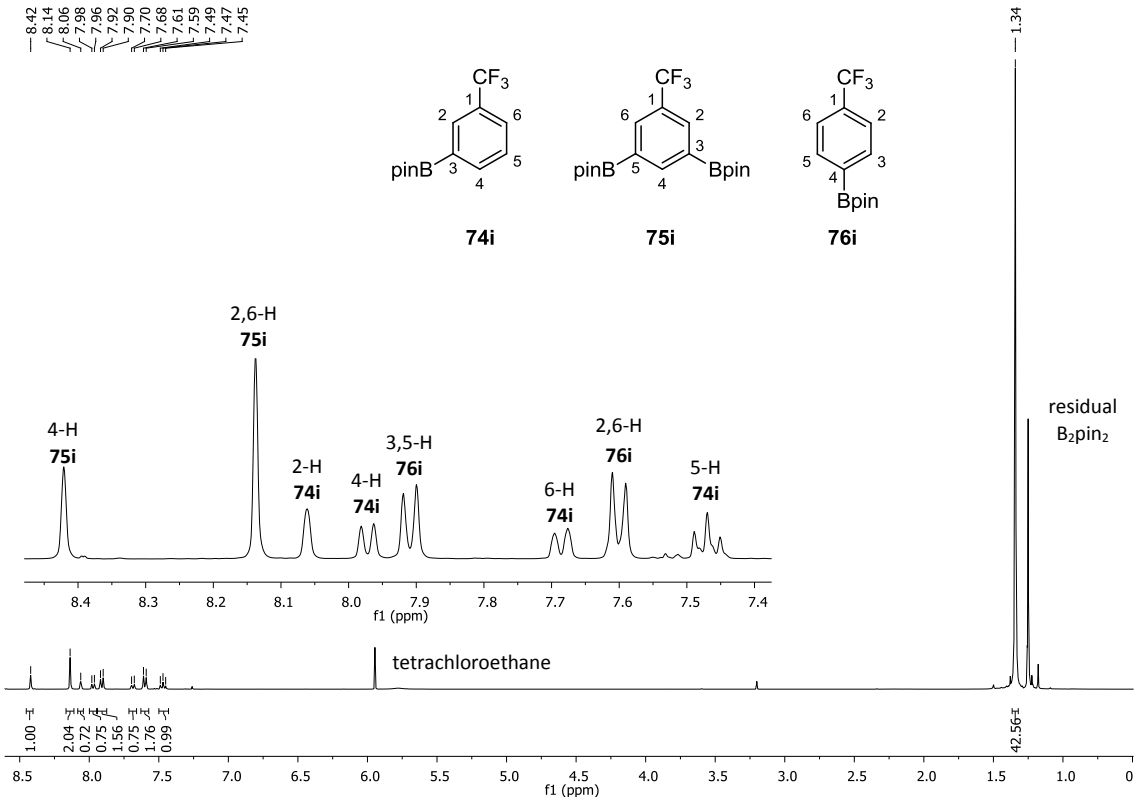
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of chlorobenzene (**73g**)



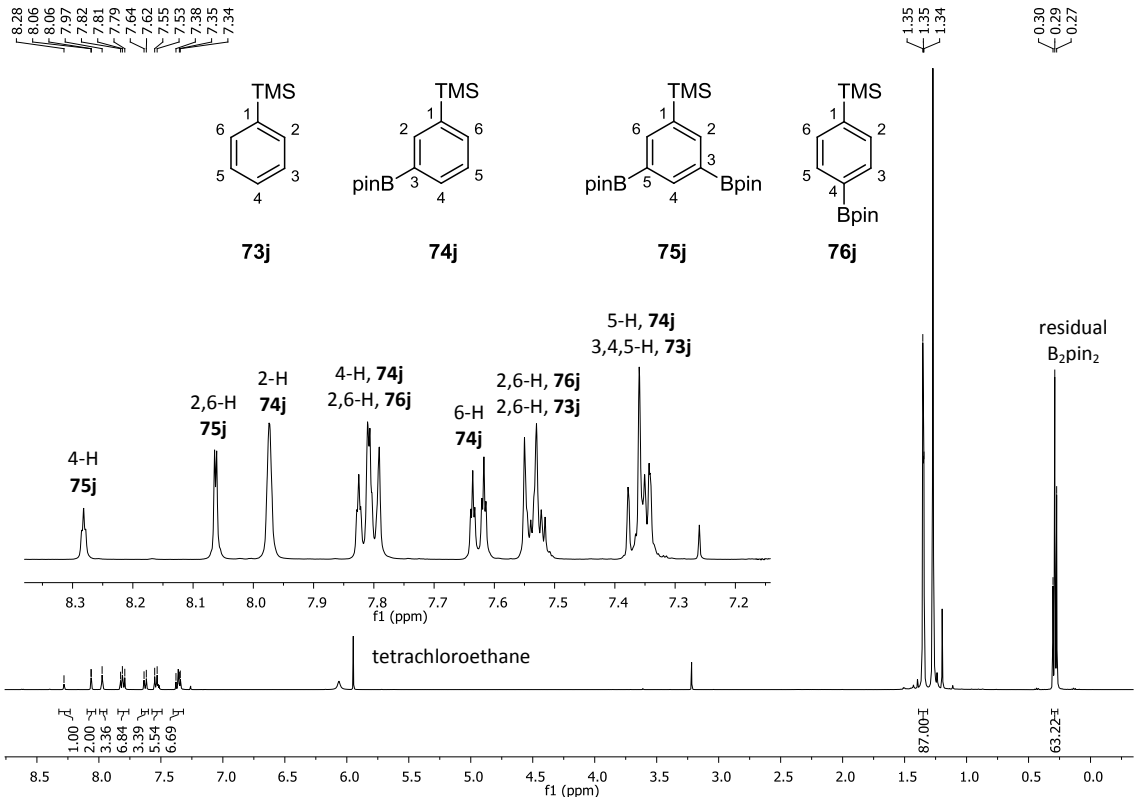
^{1}H NMR (500 MHz, acetone-d_6) - Borylation of toluene (**73h**)



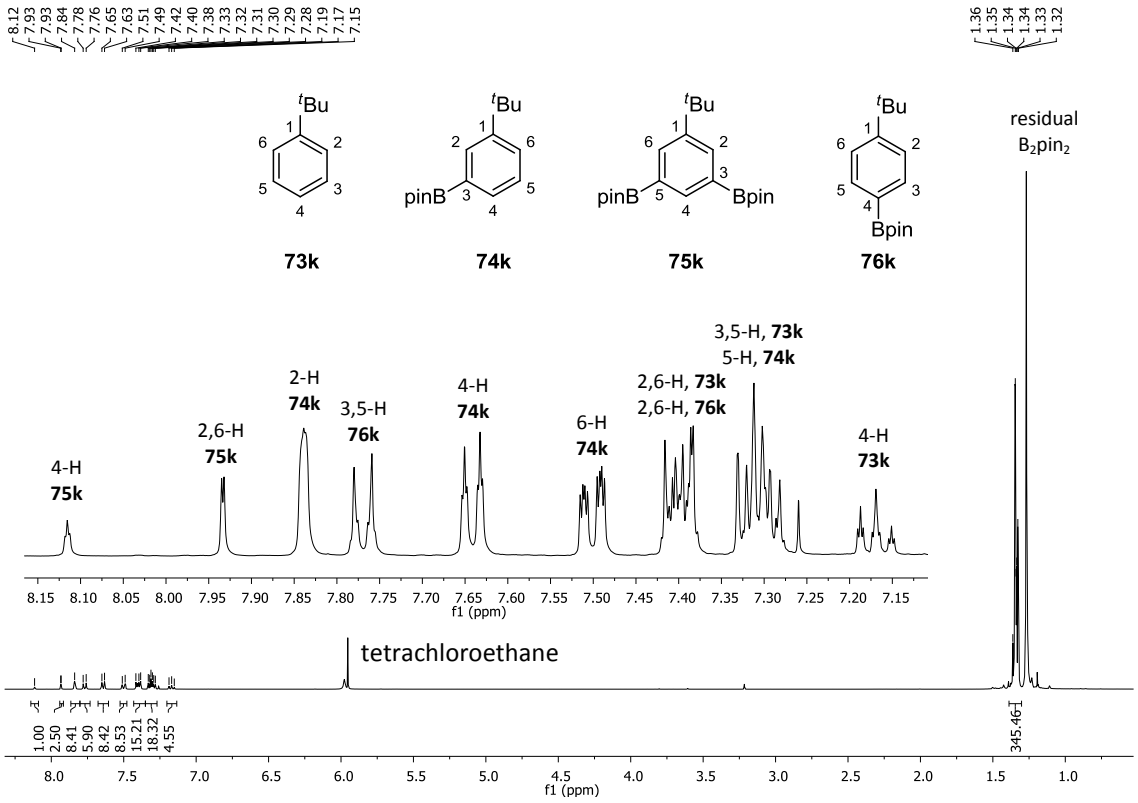
^{1}H NMR (500 MHz, $CDCl_3$) - Borylation of (trifluoromethyl)benzene (**73i**)



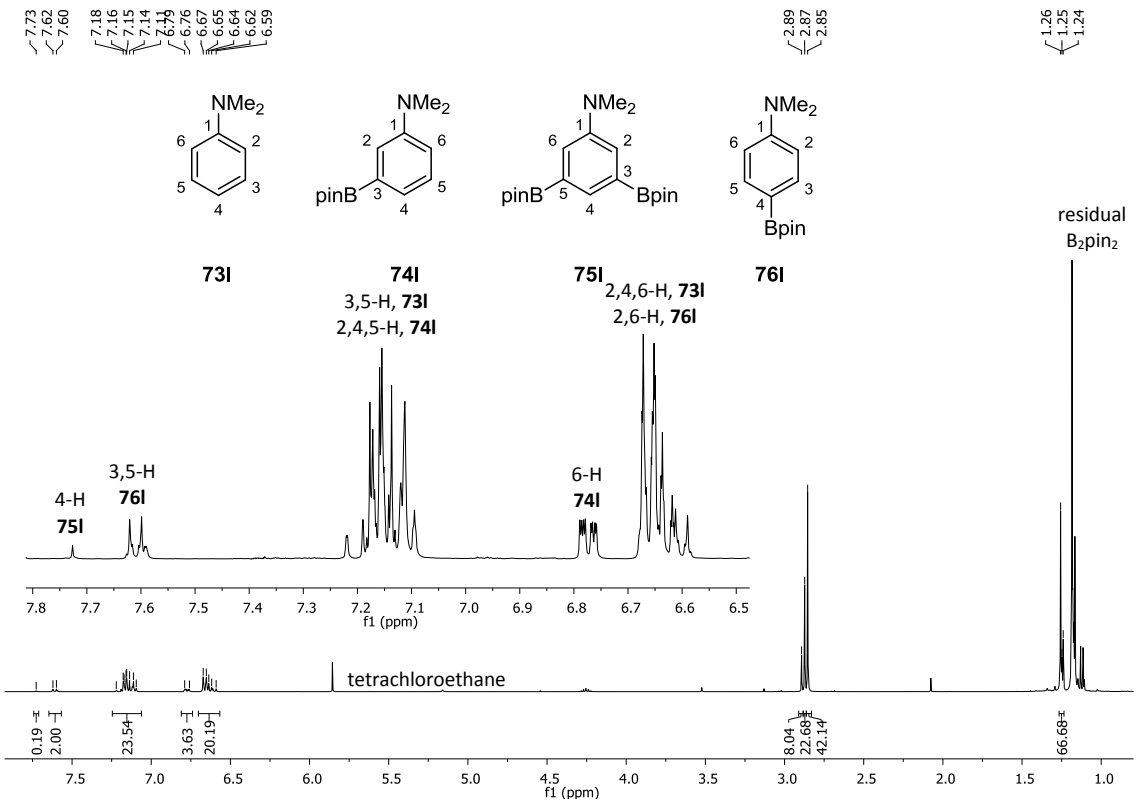
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of trimethyl(phenyl)silane (**73j**)



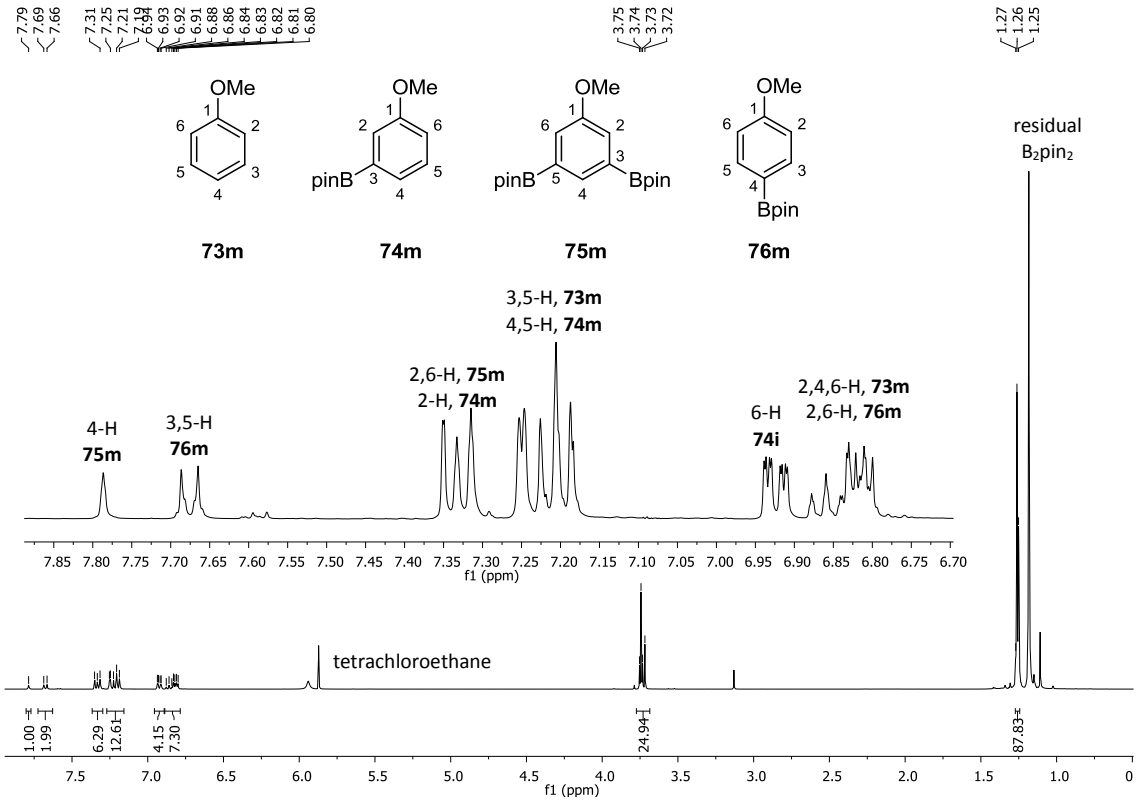
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of *tert*-butylbenzene (**73k**)



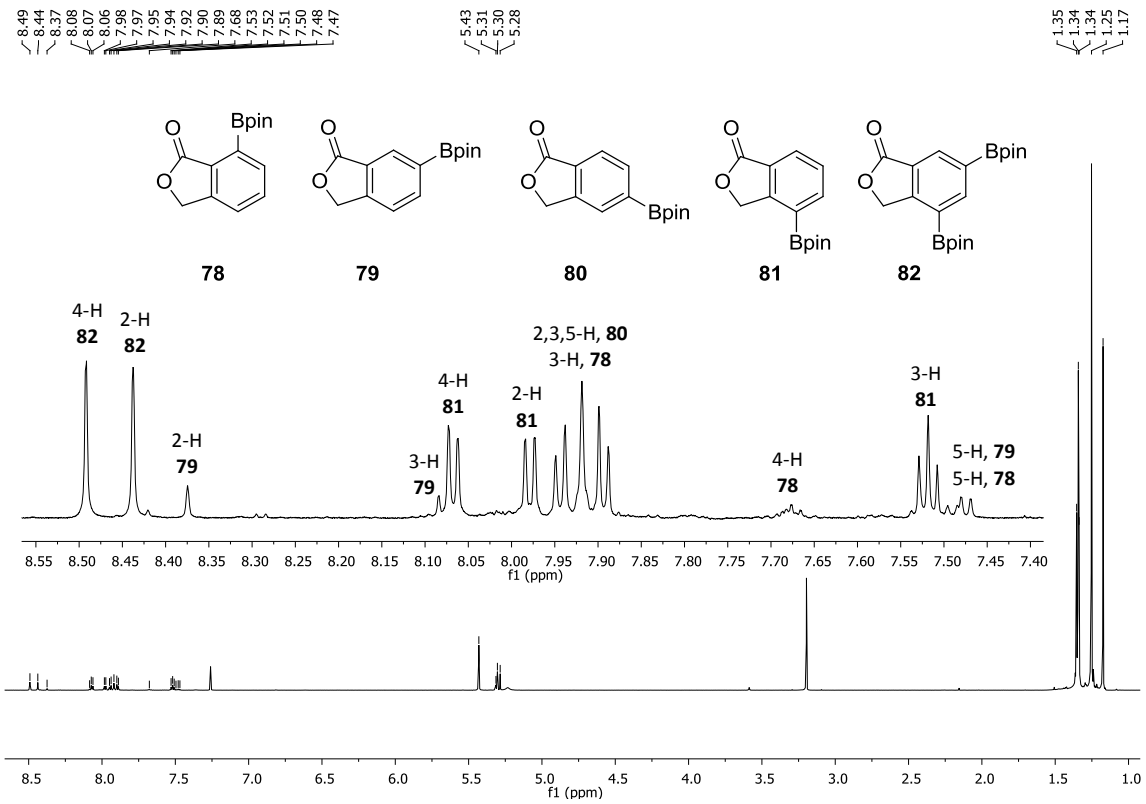
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of *N*,*N*-dimethylaniline (**73l**)



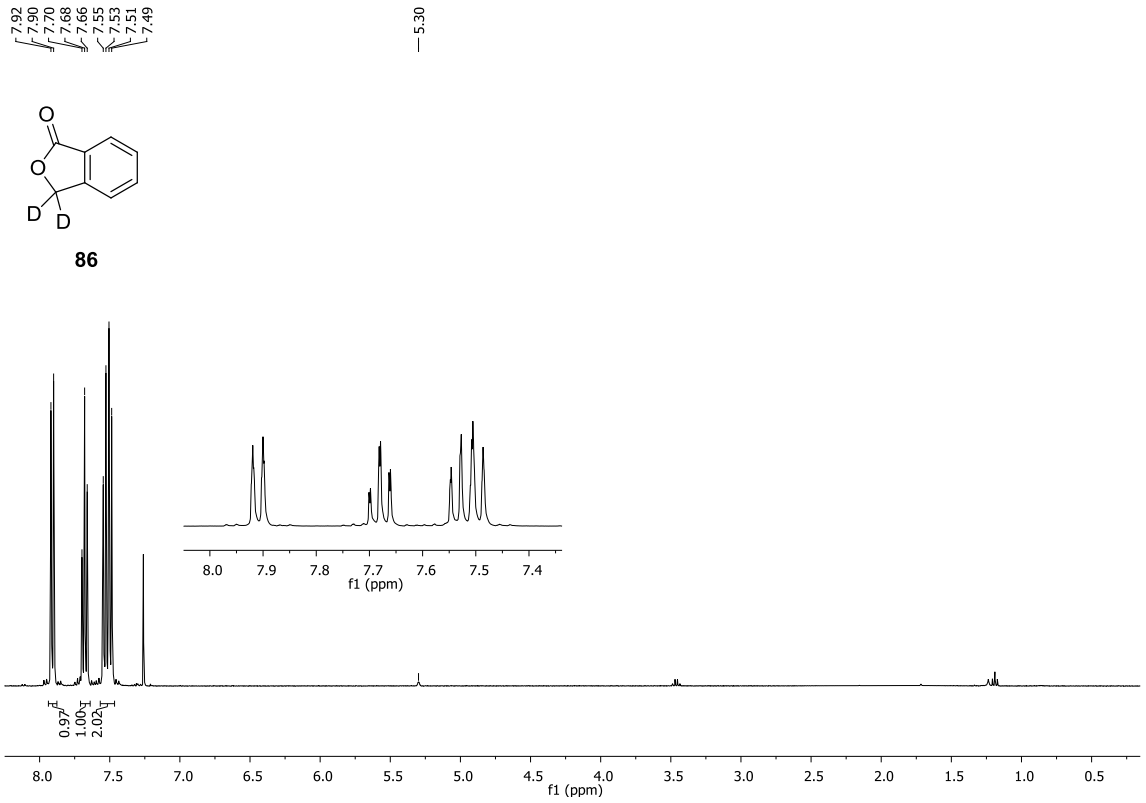
^{1}H NMR (700 MHz, $CDCl_3$) - Borylation of anisole (**73m**)



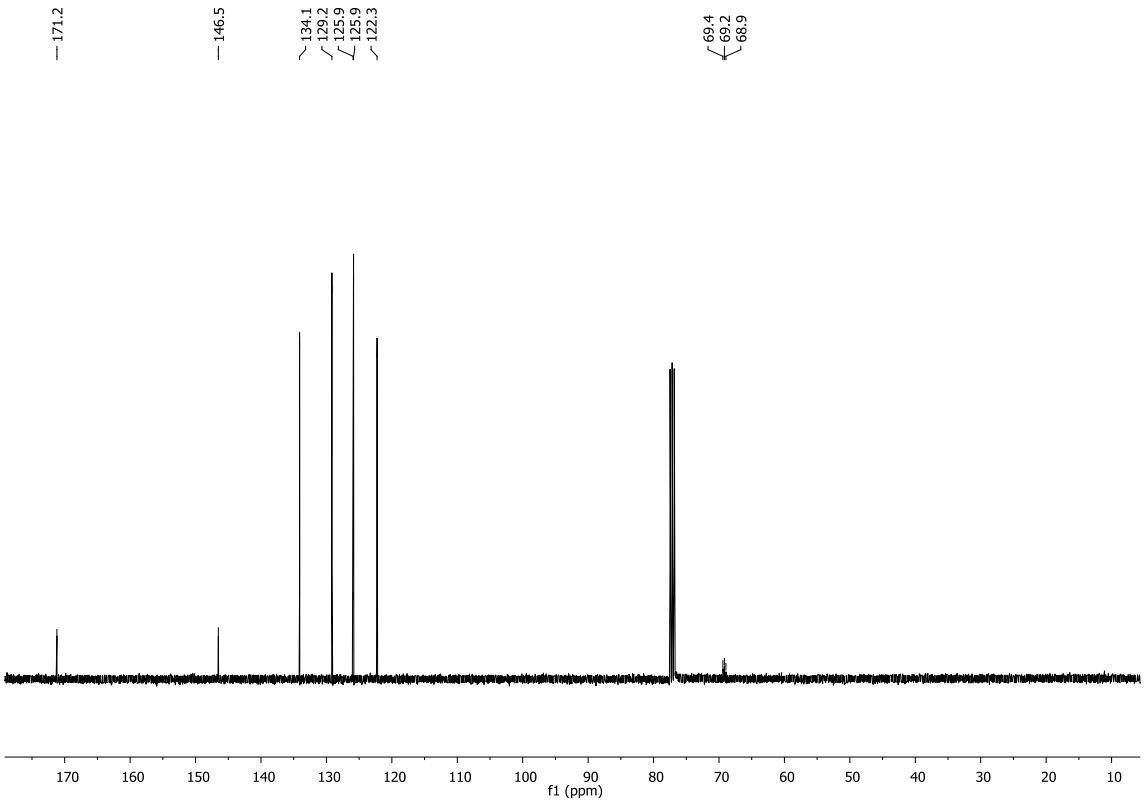
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of phthalide (**77**)



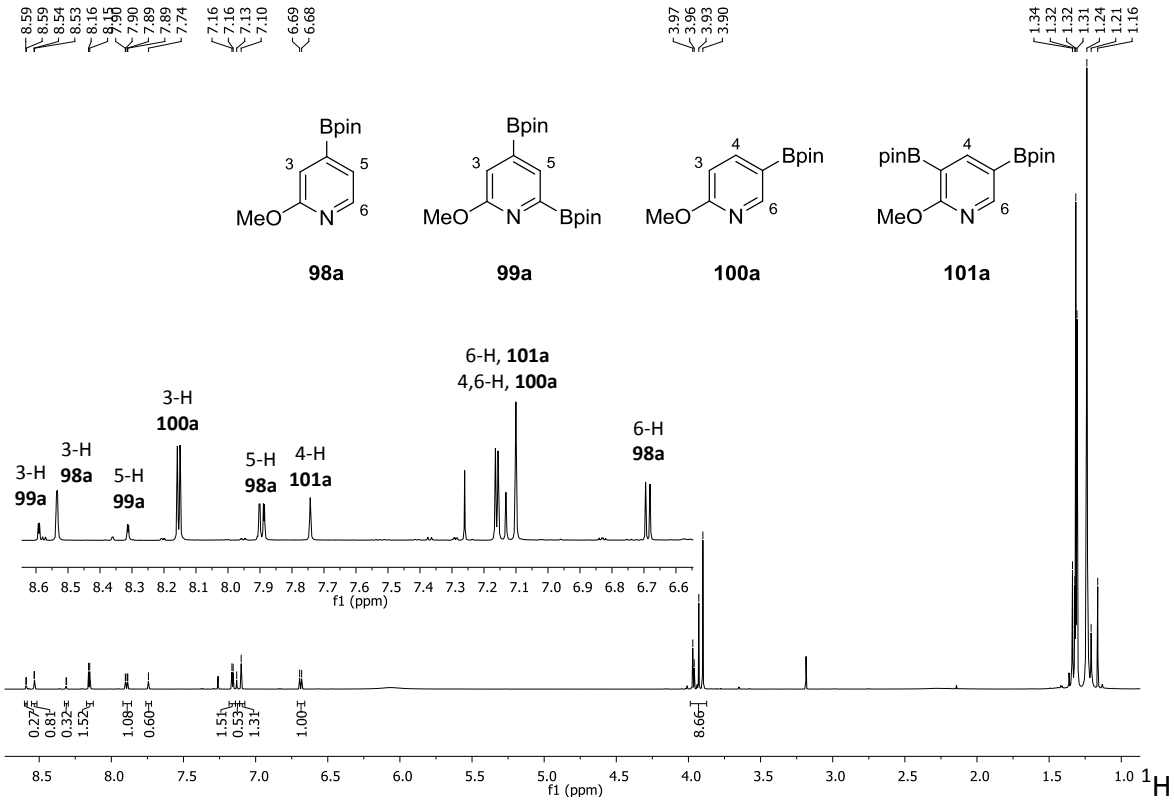
^{1}H NMR (400 MHz, $CDCl_3$) – **86**



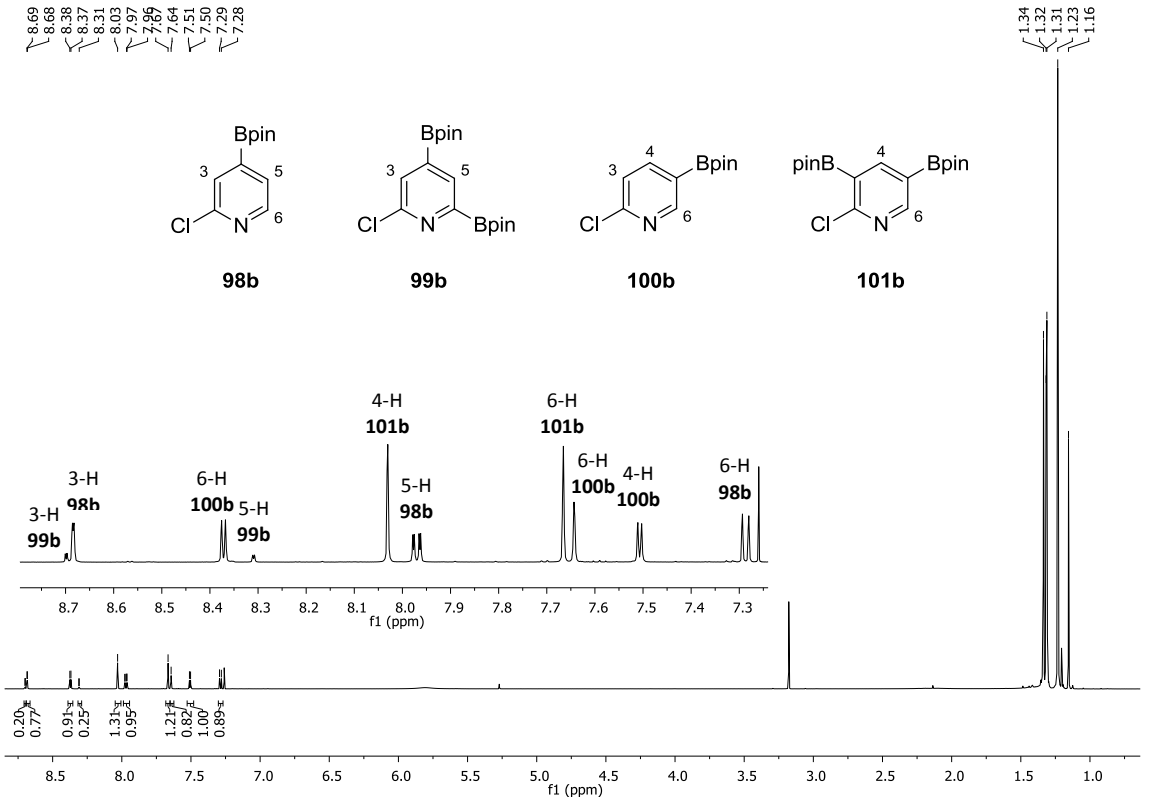
^{13}C NMR (101 MHz, $CDCl_3$) - **86**



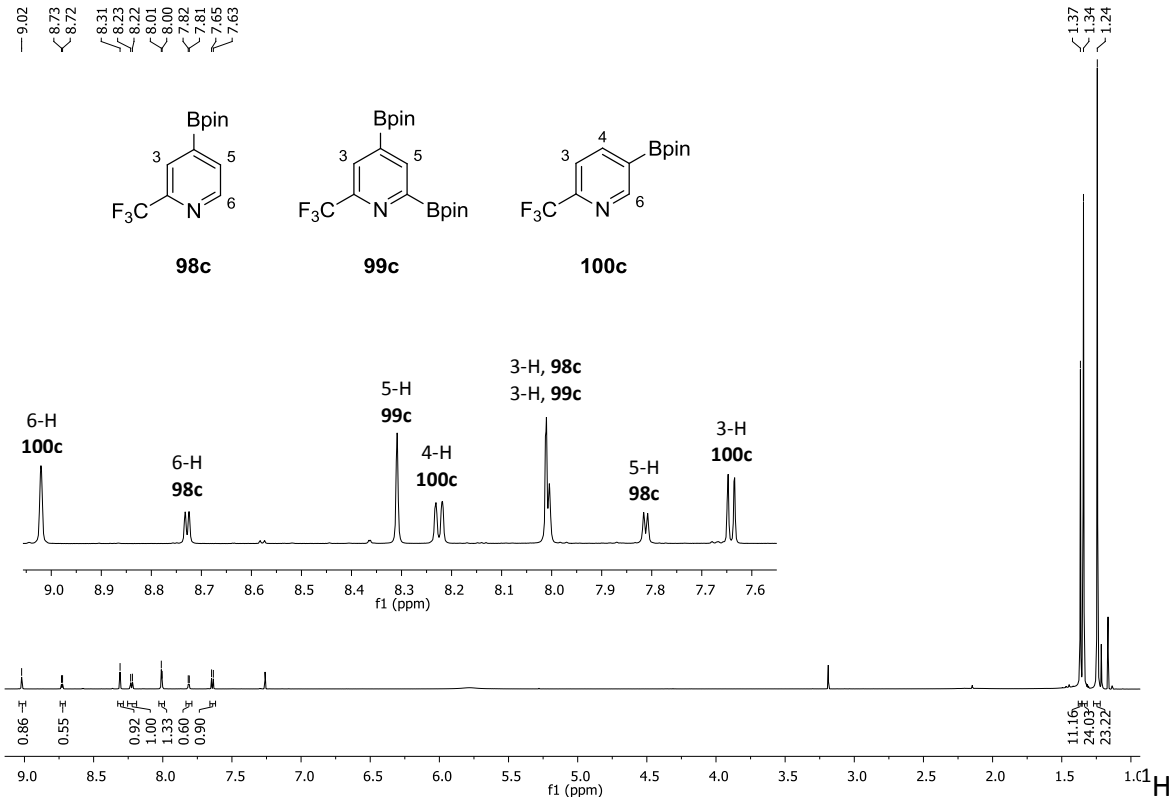
^{1}H NMR (600 MHz, $CDCl_3$) - Borylation of 2-methoxy pyridine (**97a**)



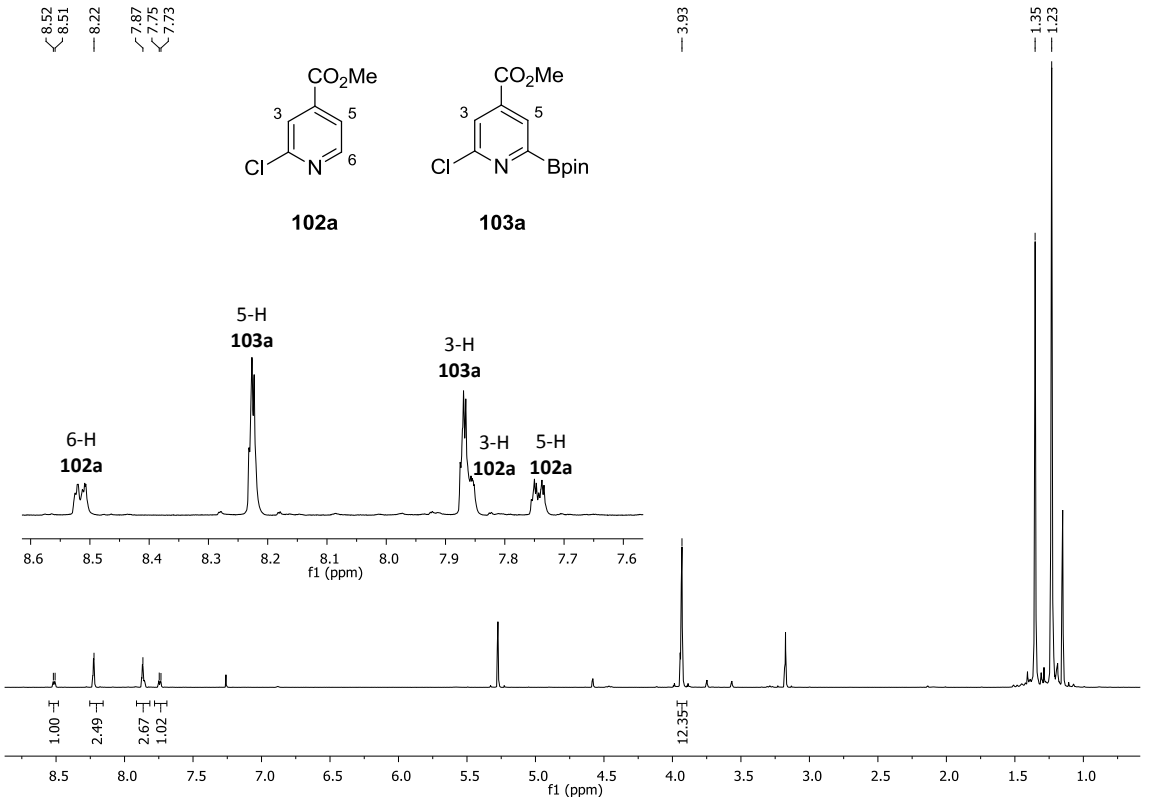
NMR (600 MHz, $CDCl_3$) - Borylation of 2-chloro pyridine (**97b**)



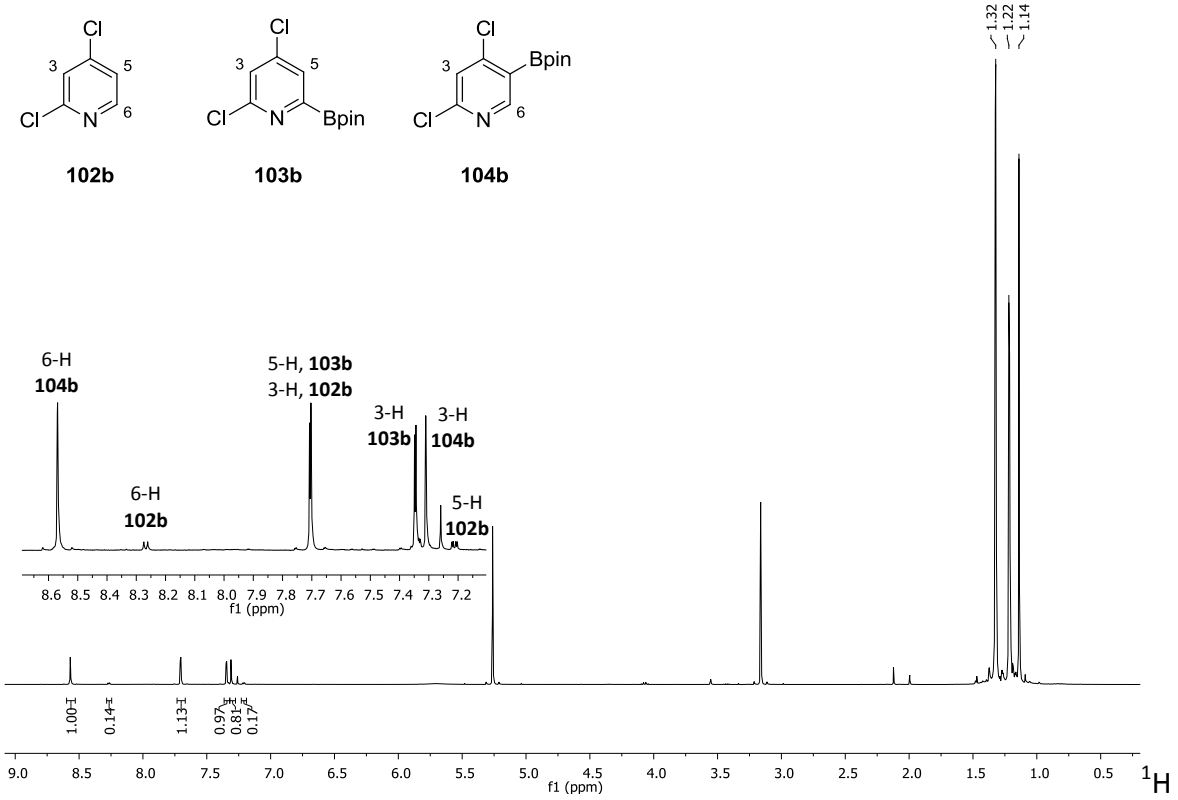
^{1}H NMR (600 MHz, $CDCl_3$) - Borylation of 2-(trifluoromethyl) pyridine (**87c**)



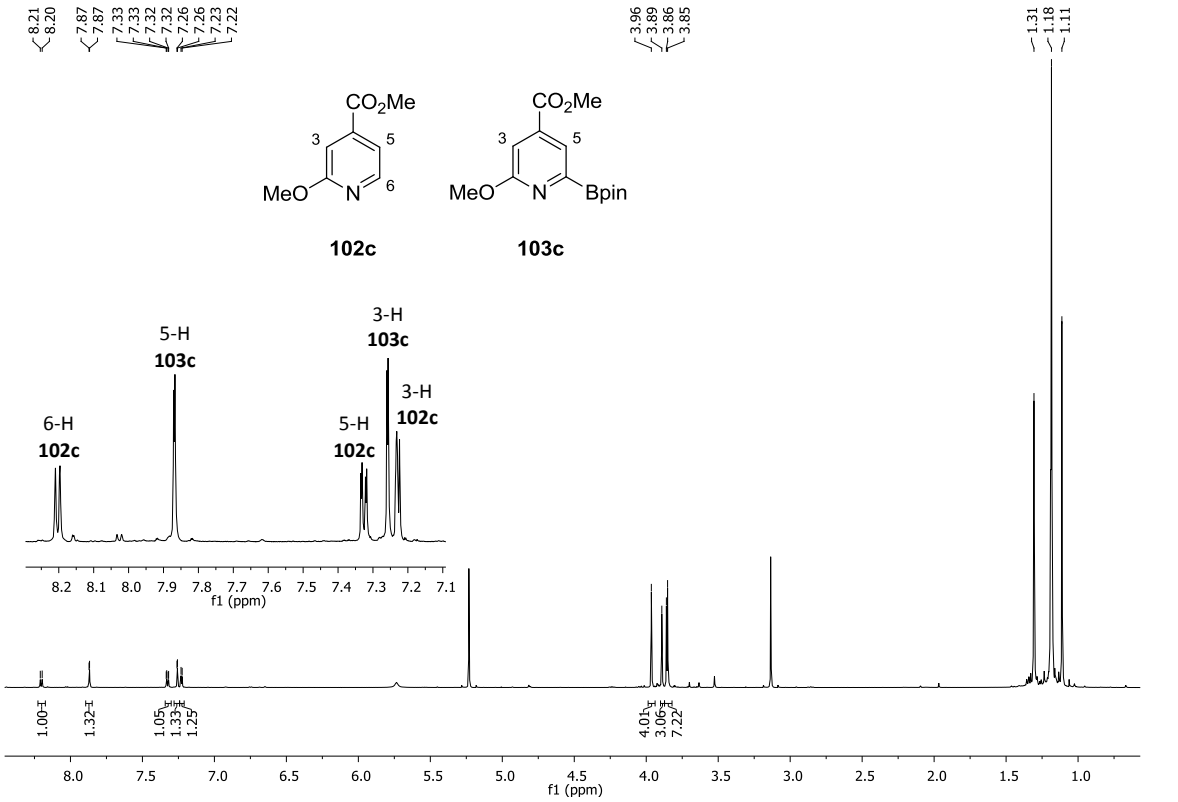
NMR (400 MHz, $CDCl_3$) - Borylation of methyl 2-chloroisonicotinate (**102a**)



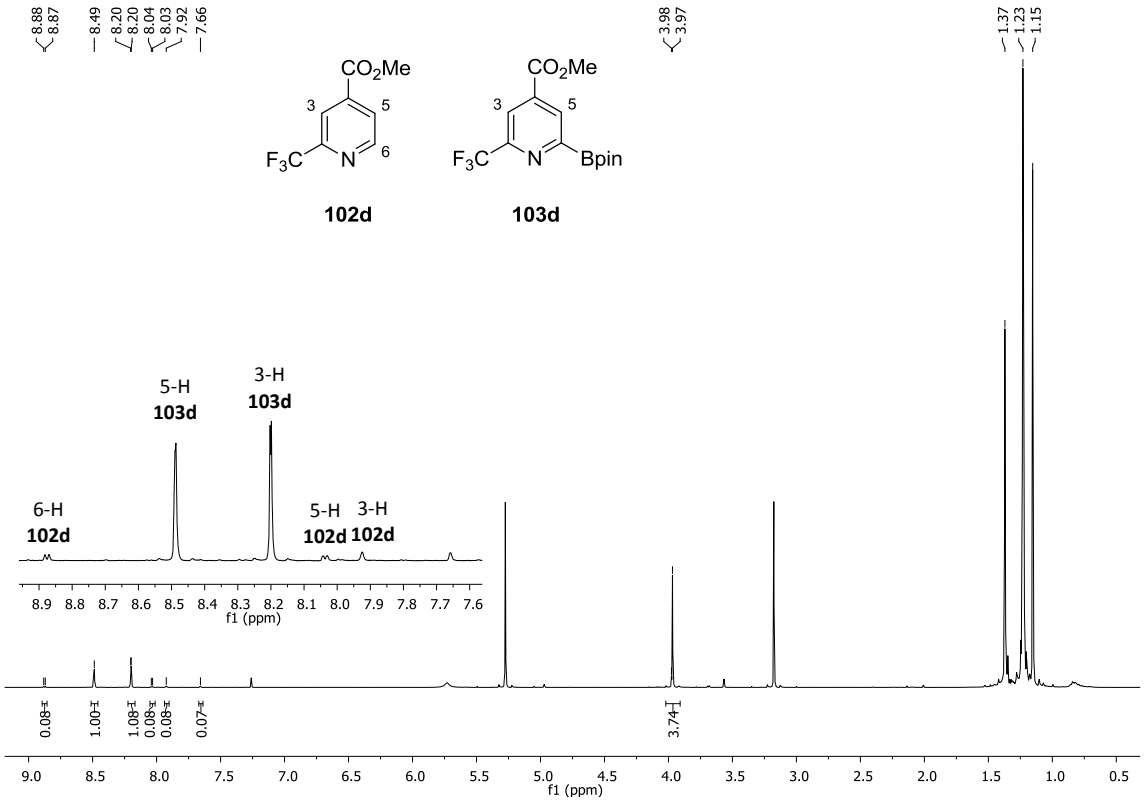
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 2,4-dichloropyridine (**102b**)



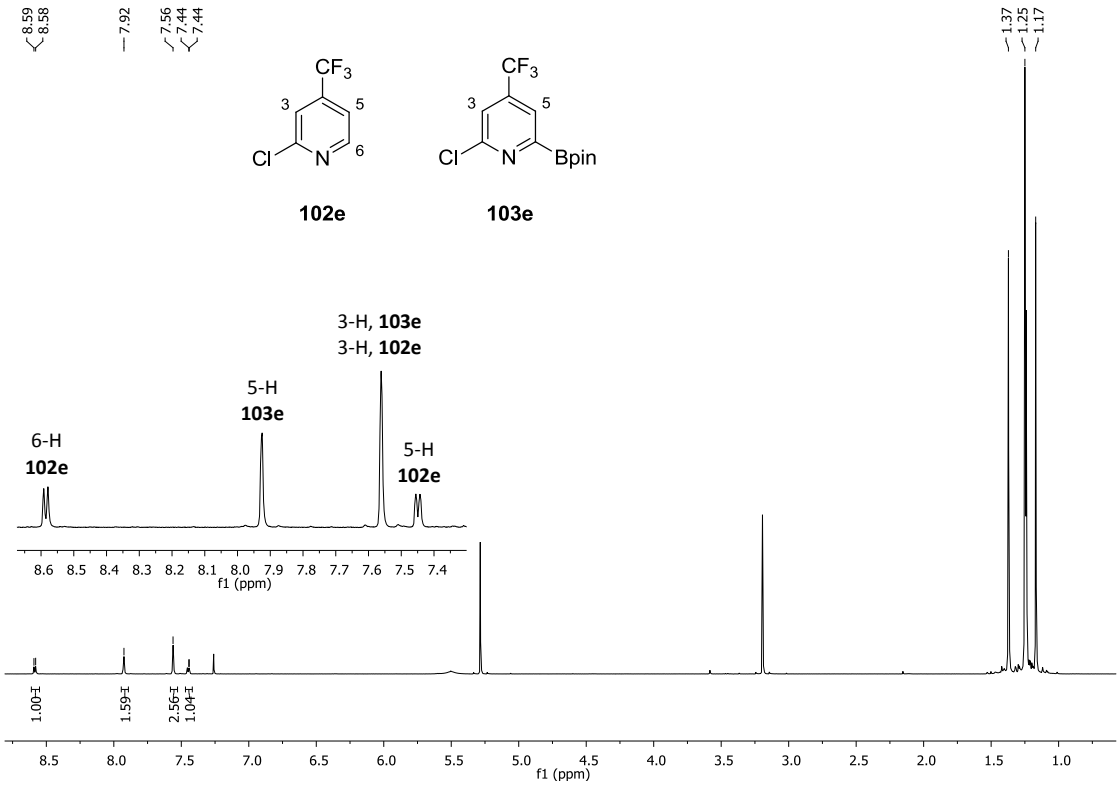
NMR (400 MHz, $CDCl_3$) - Borylation of methyl 2-methoxyisonicotinate (**102c**)



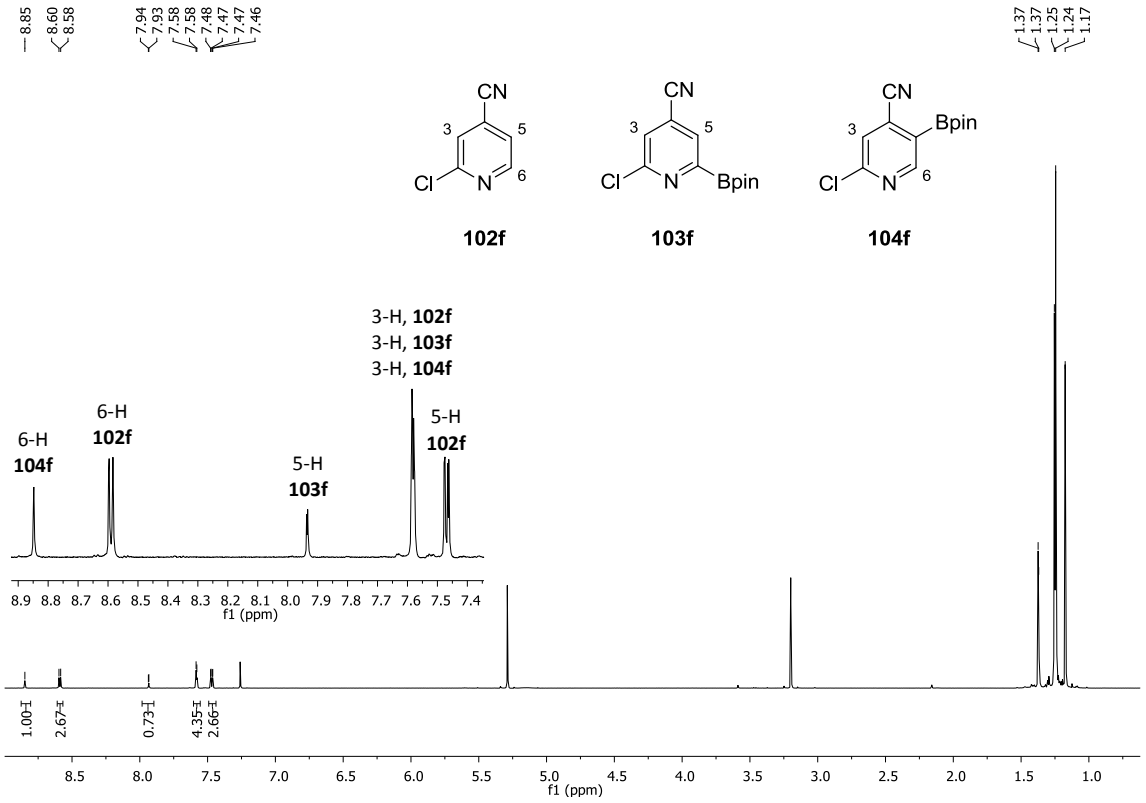
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of methyl 2-(trifluoromethyl)isonicotinate (**102d**)



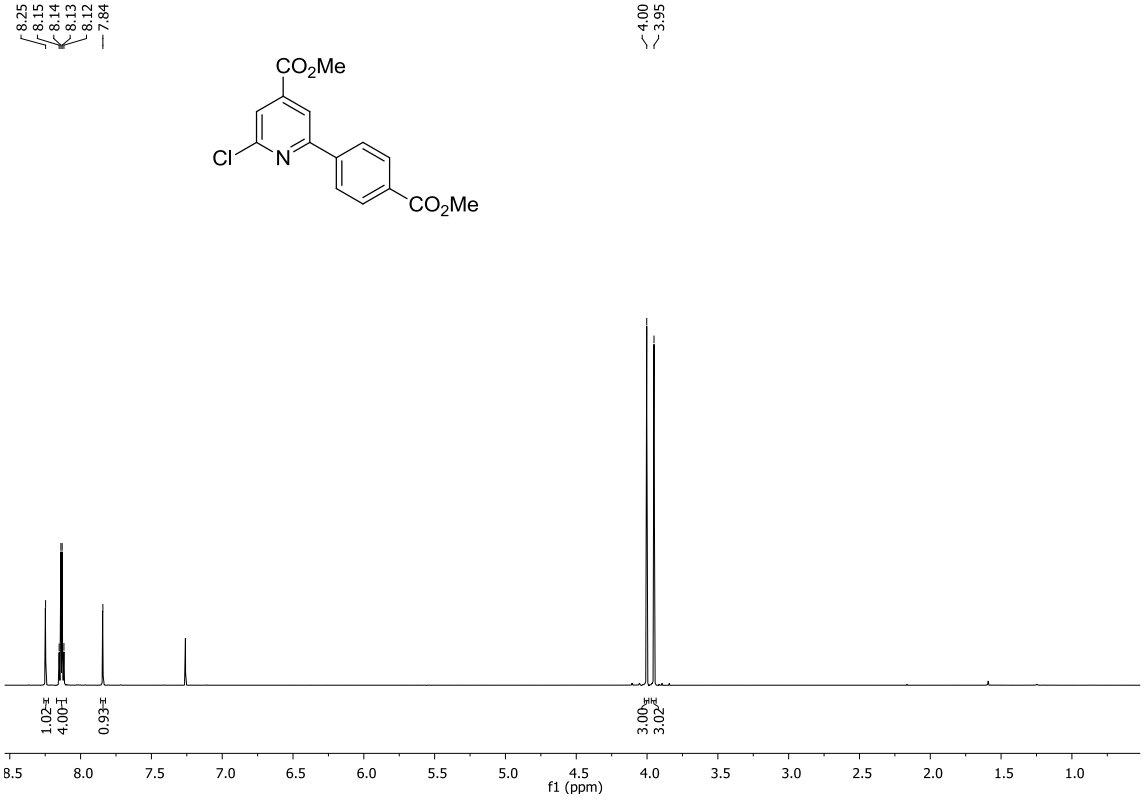
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 2-chloro-4-(trifluoromethyl)pyridine (**102e**)



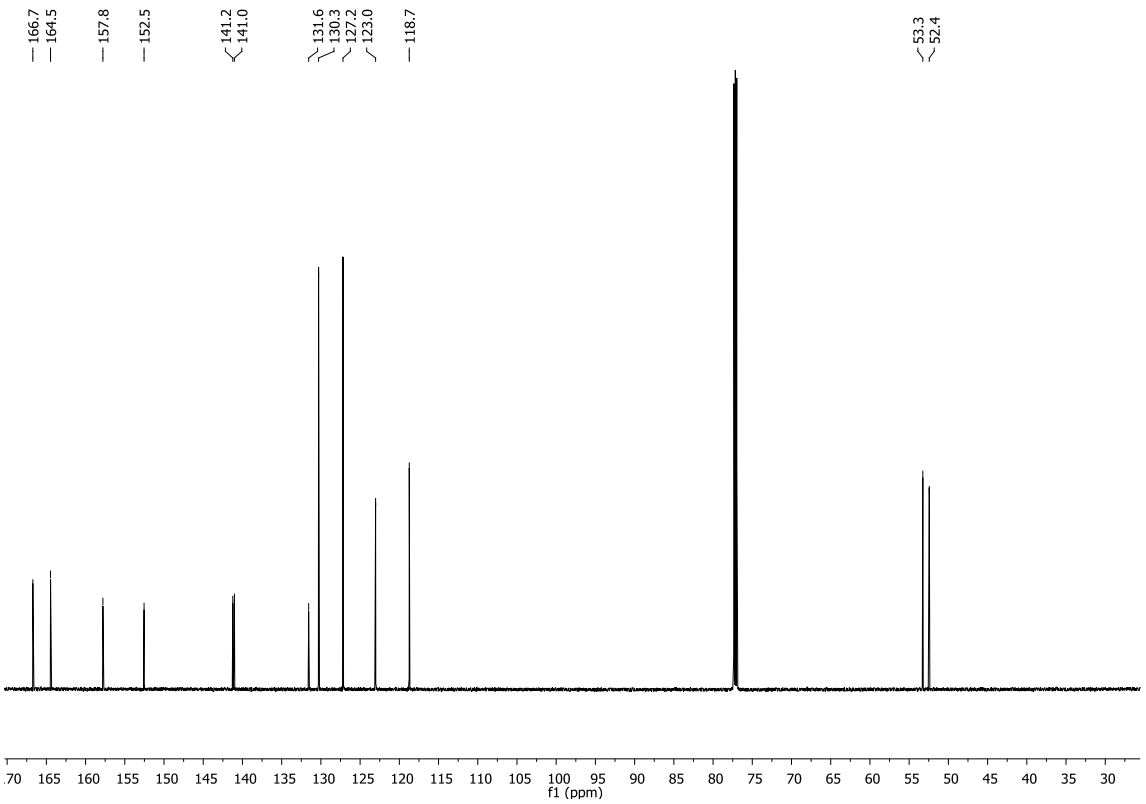
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of 2-chloroisonicotinonitrile (**102f**)



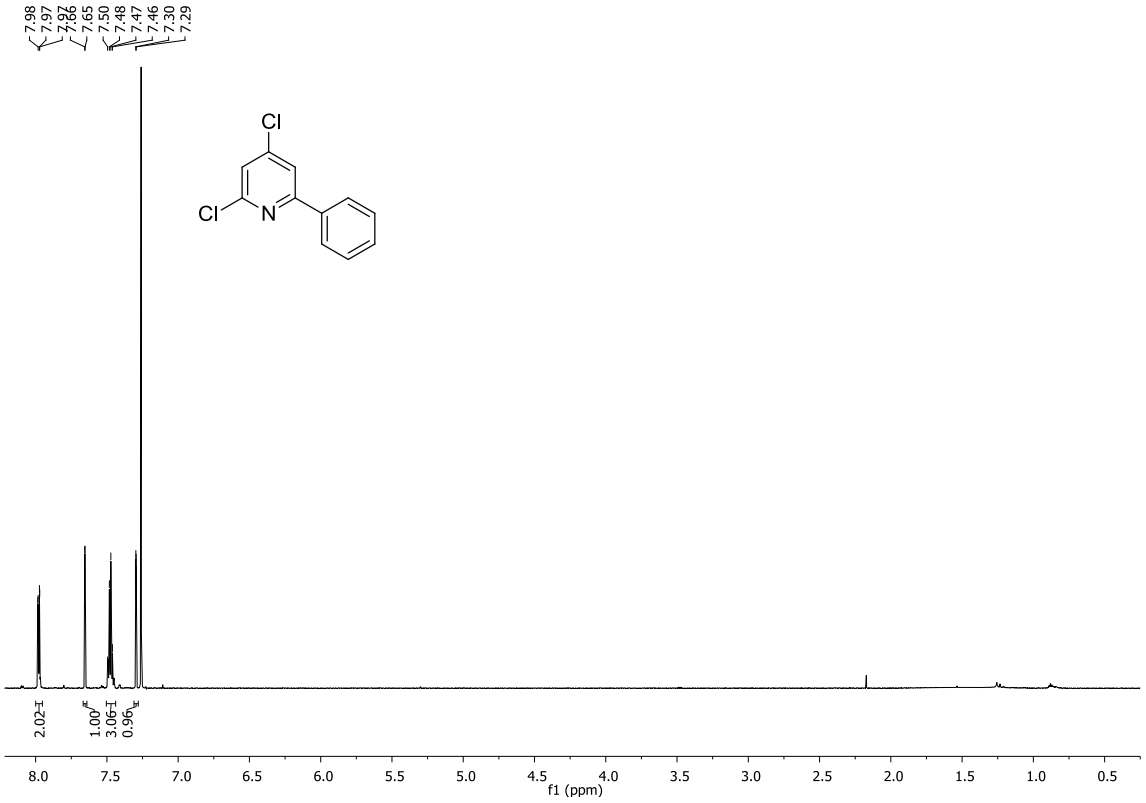
^{1}H NMR (700 MHz, $CDCl_3$) – **106**



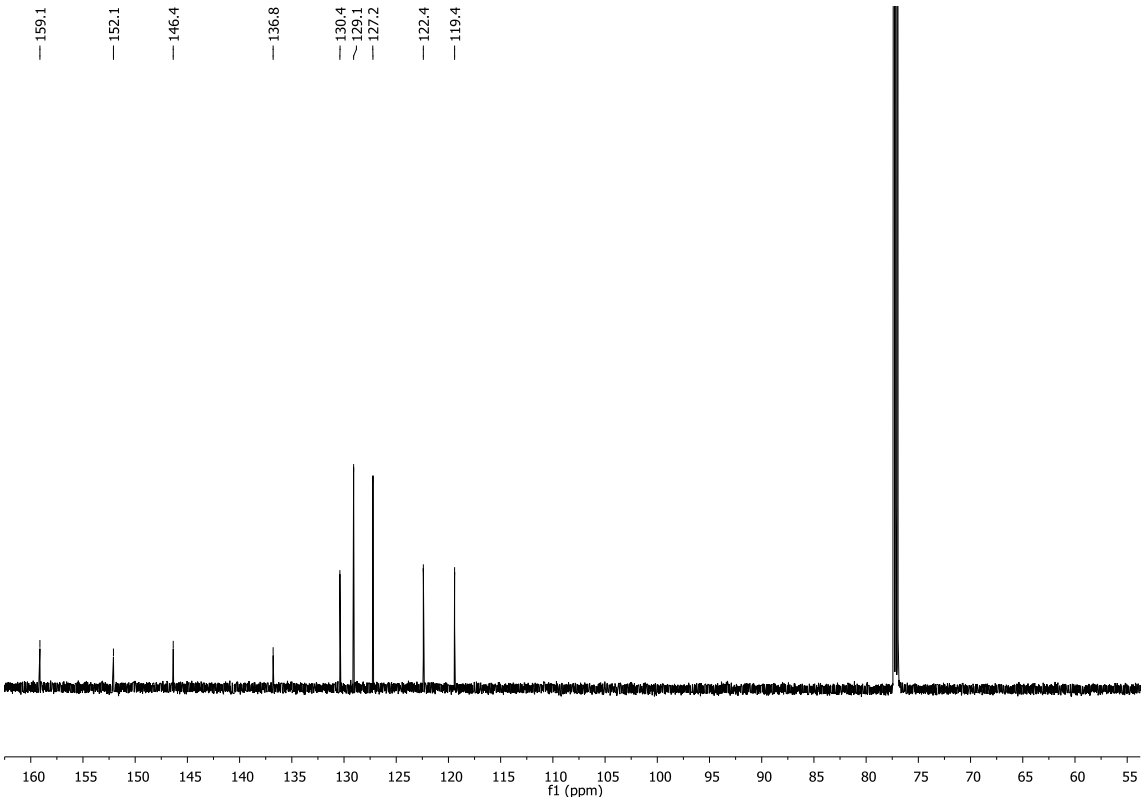
^{13}C NMR (176 MHz, $CDCl_3$) – **106**



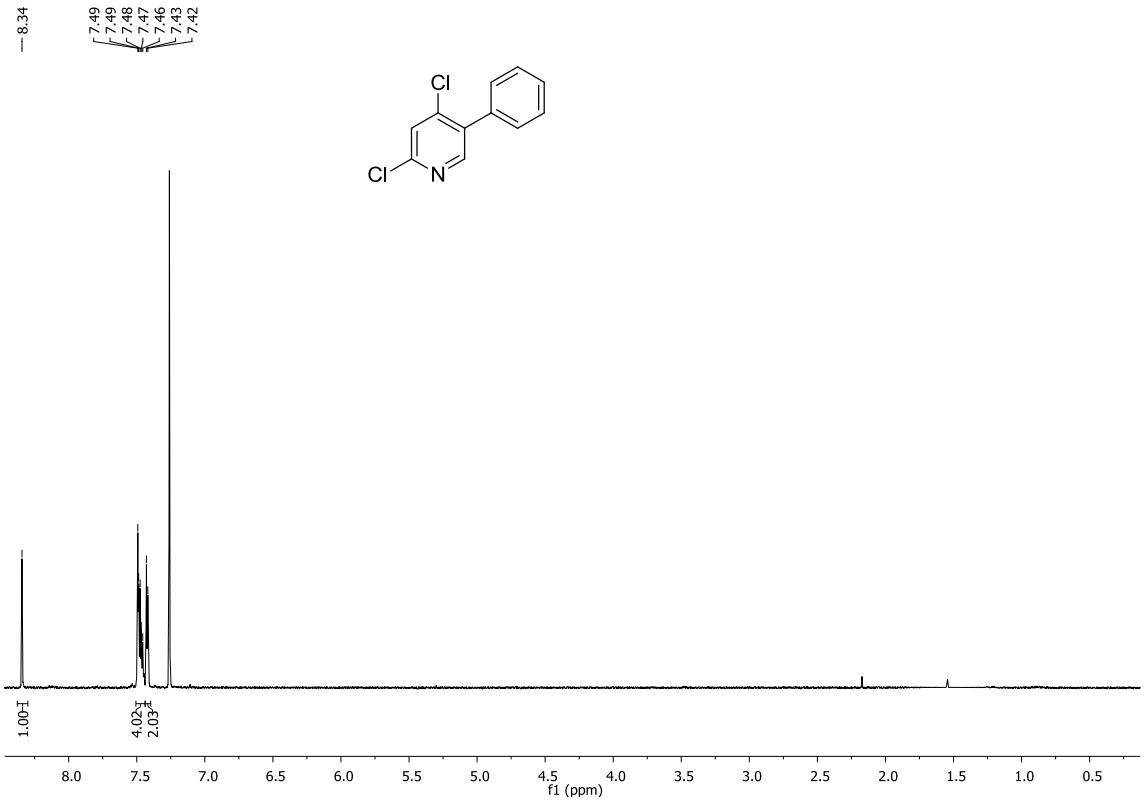
^{1}H NMR (700 MHz, $CDCl_3$) – **109b**



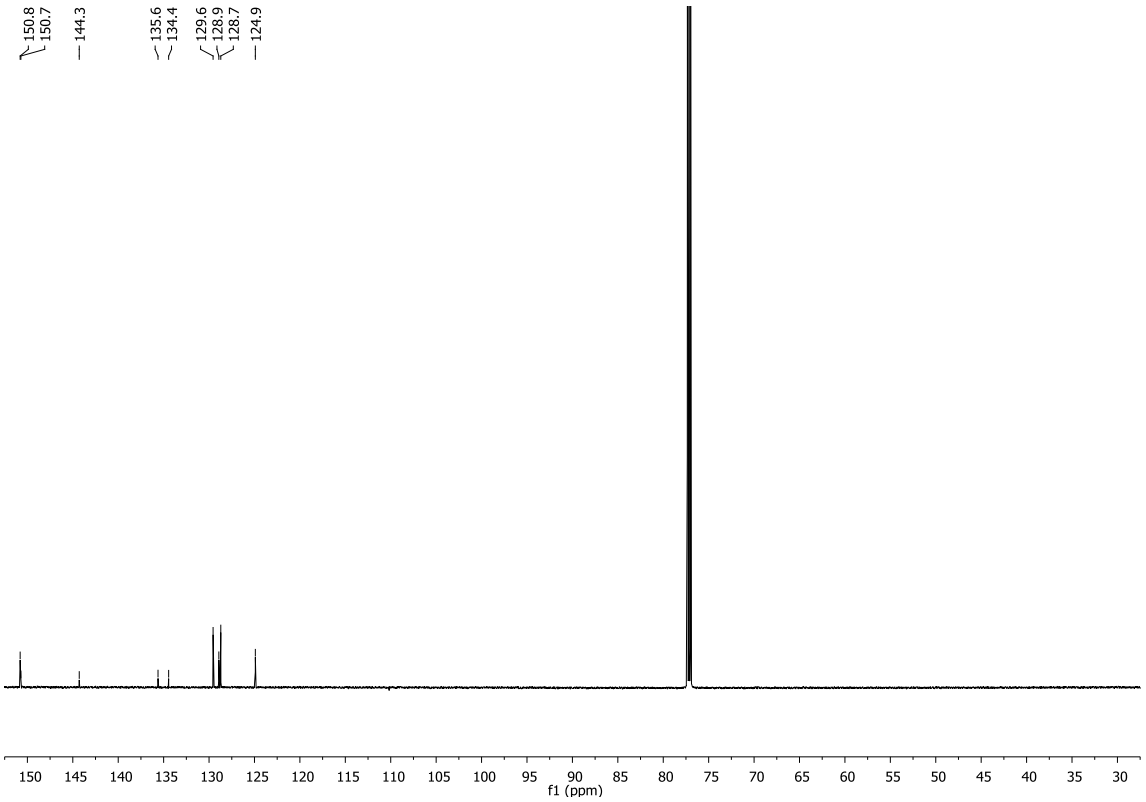
^{13}C NMR (176 MHz, $CDCl_3$) – **109b**



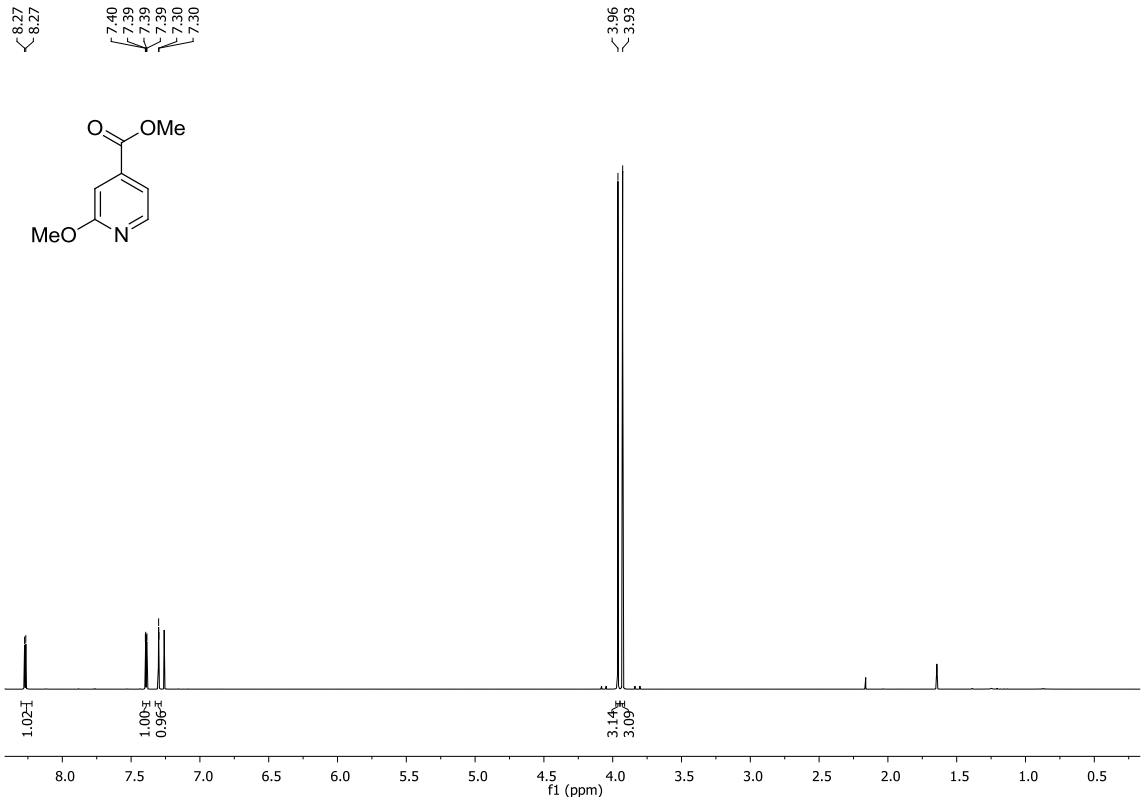
^{1}H NMR (700 MHz, $CDCl_3$) – **110b**



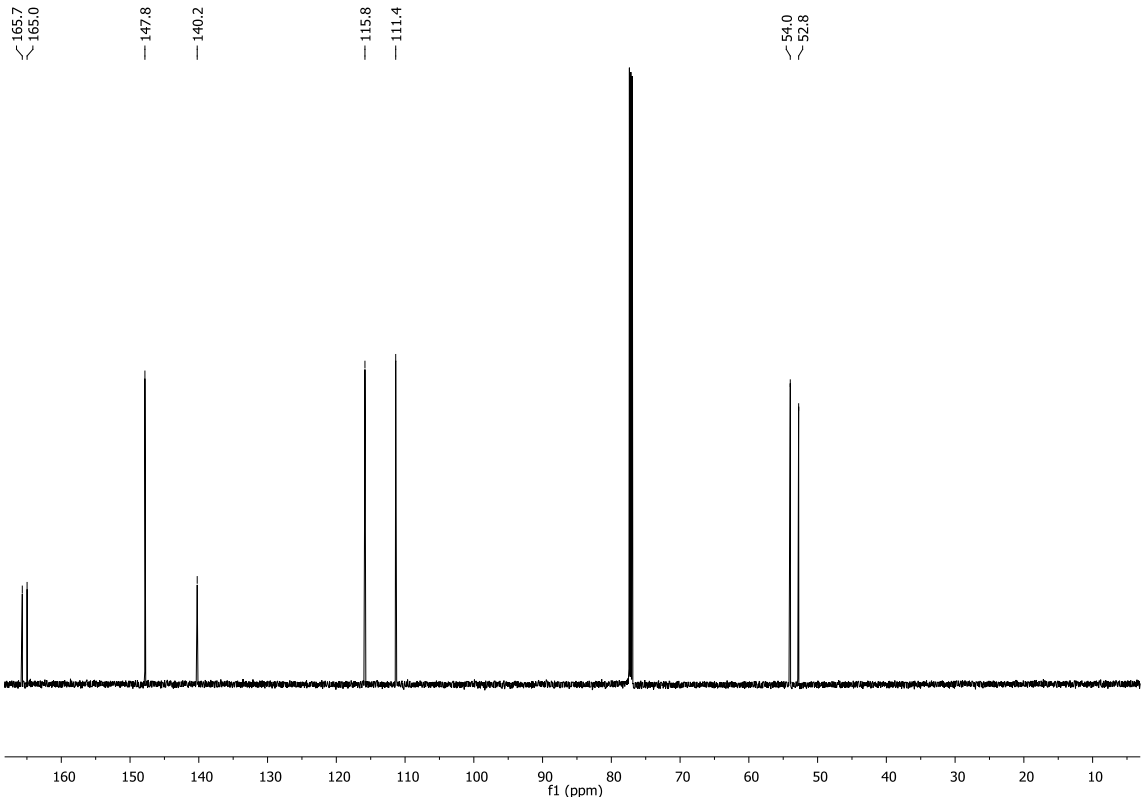
^{13}C NMR (176 MHz, $CDCl_3$) – **110b**



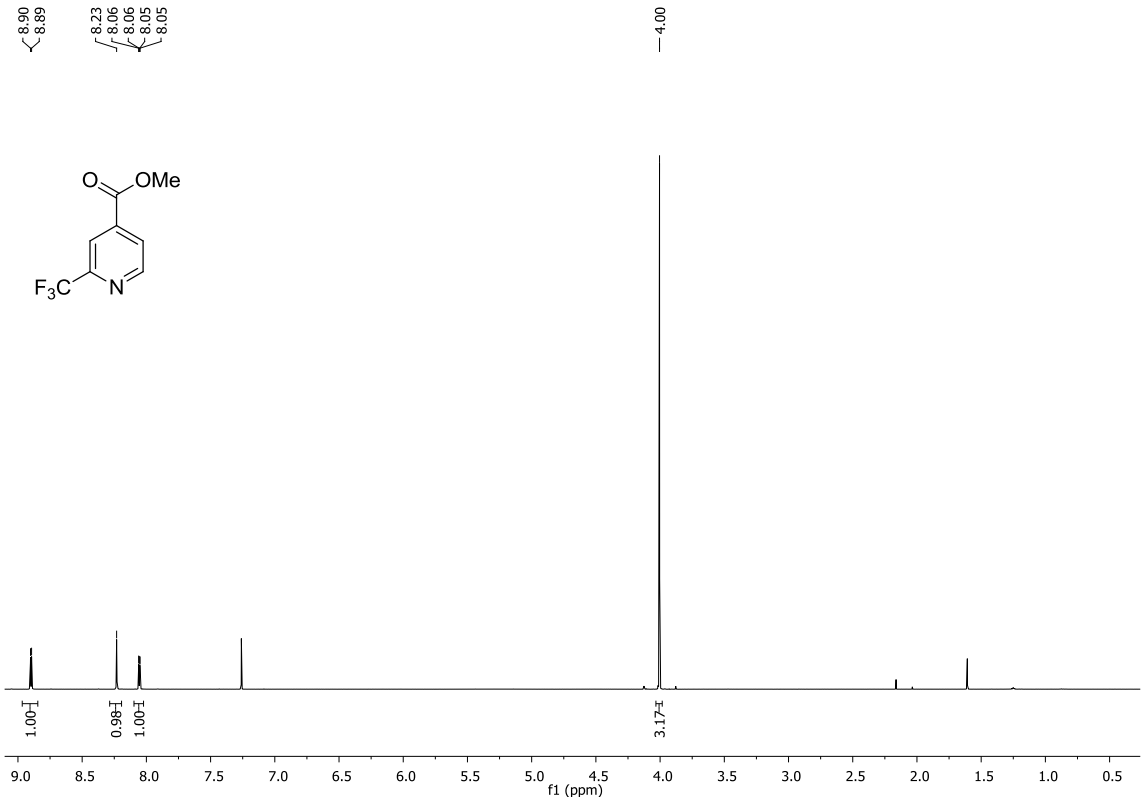
^{1}H NMR (600 MHz, $CDCl_3$) – **102c**



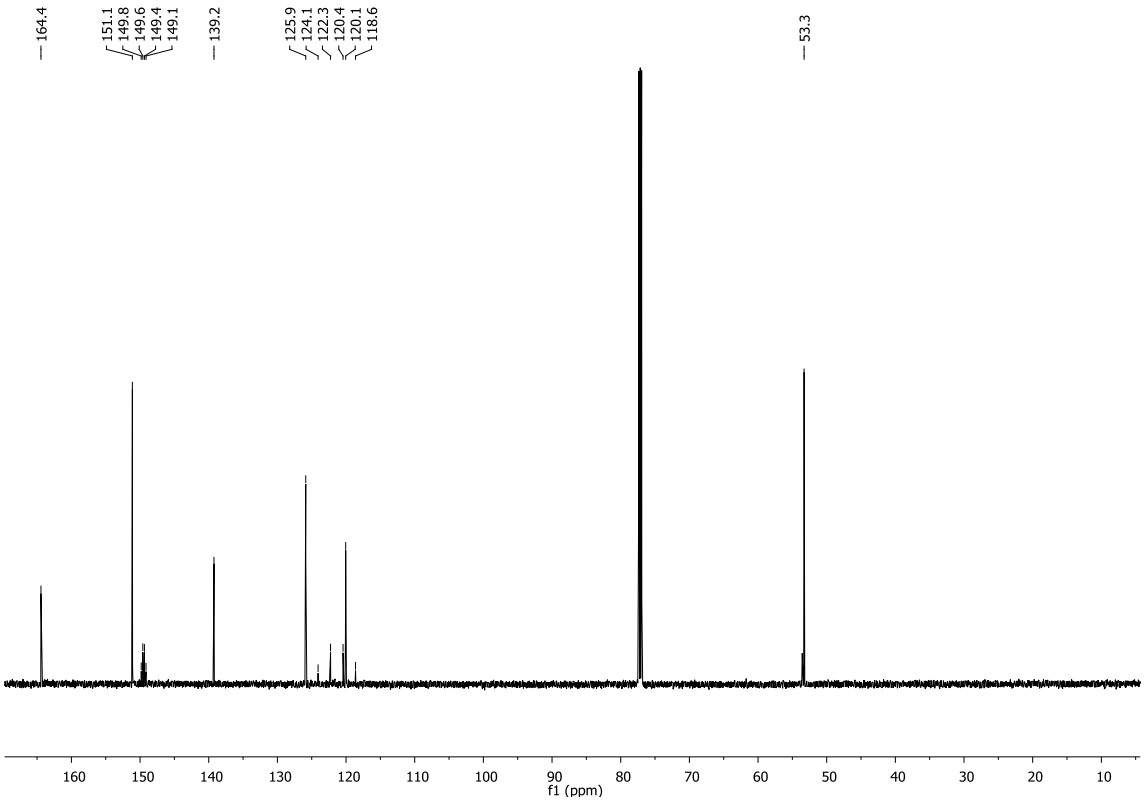
^{13}C NMR (151 MHz, $CDCl_3$) – **102c**



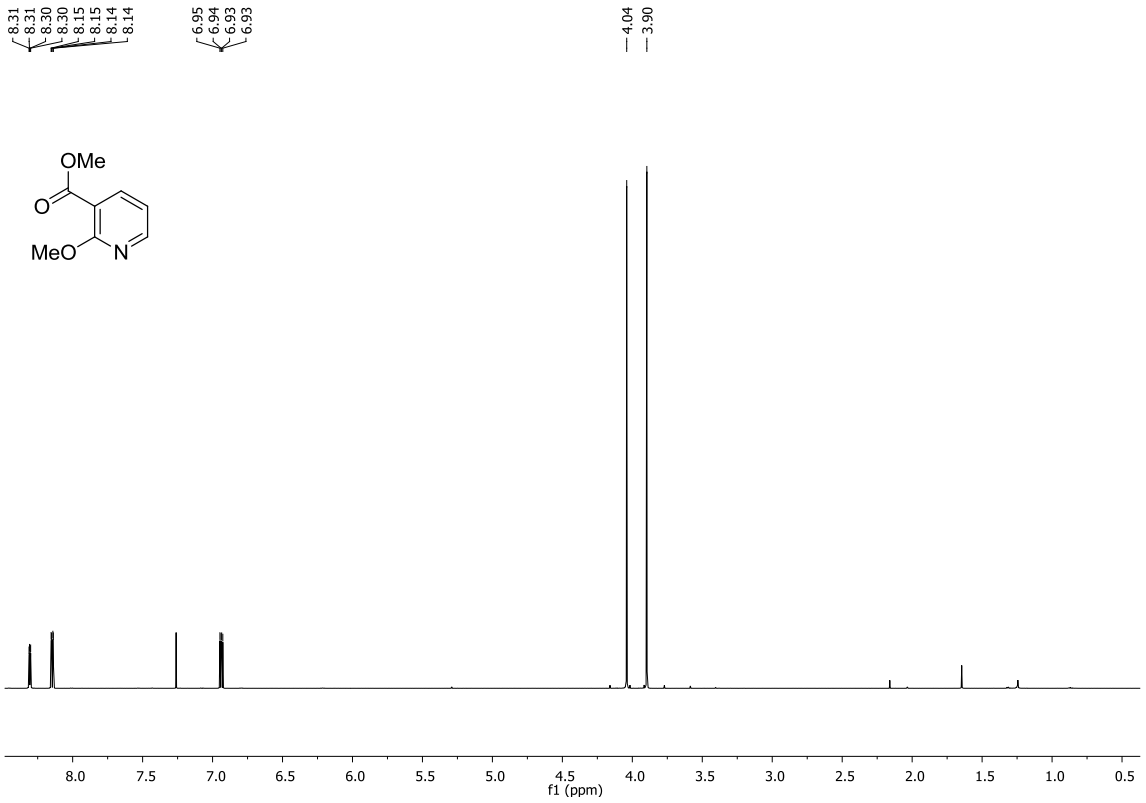
^{1}H NMR (600 MHz, $CDCl_3$) – **102d**



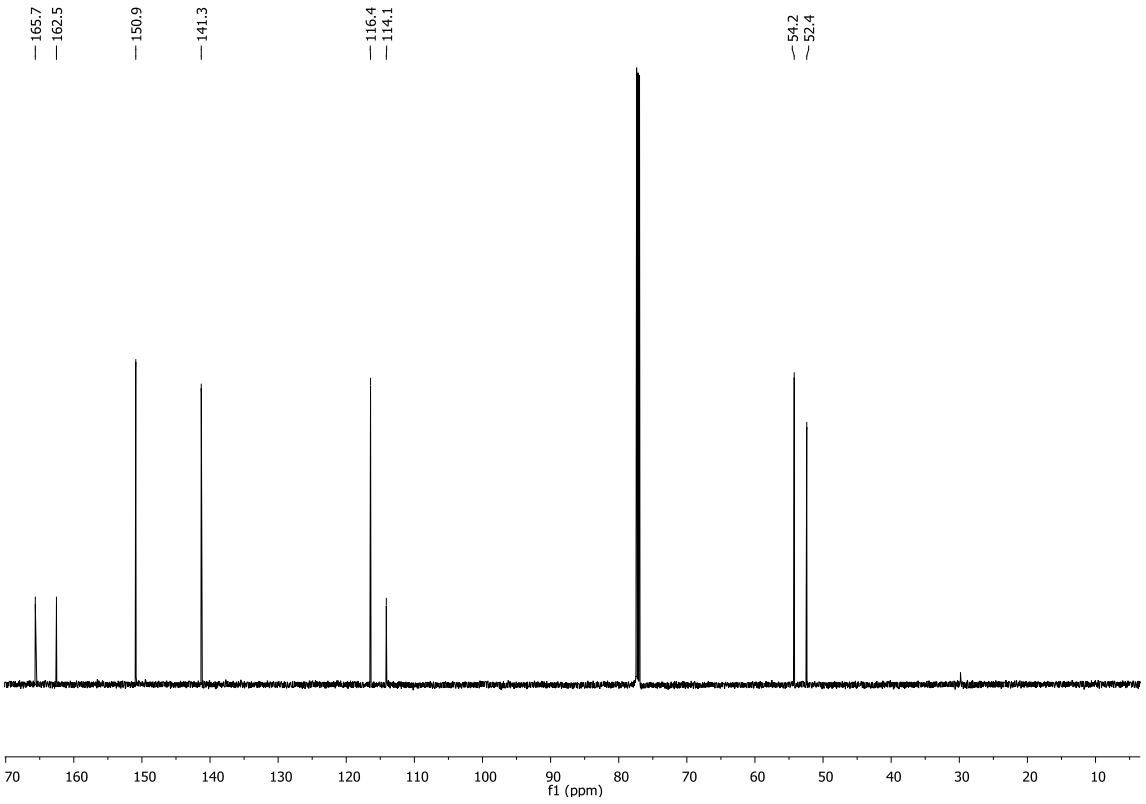
^{13}C NMR (151 MHz, $CDCl_3$) – **102d**



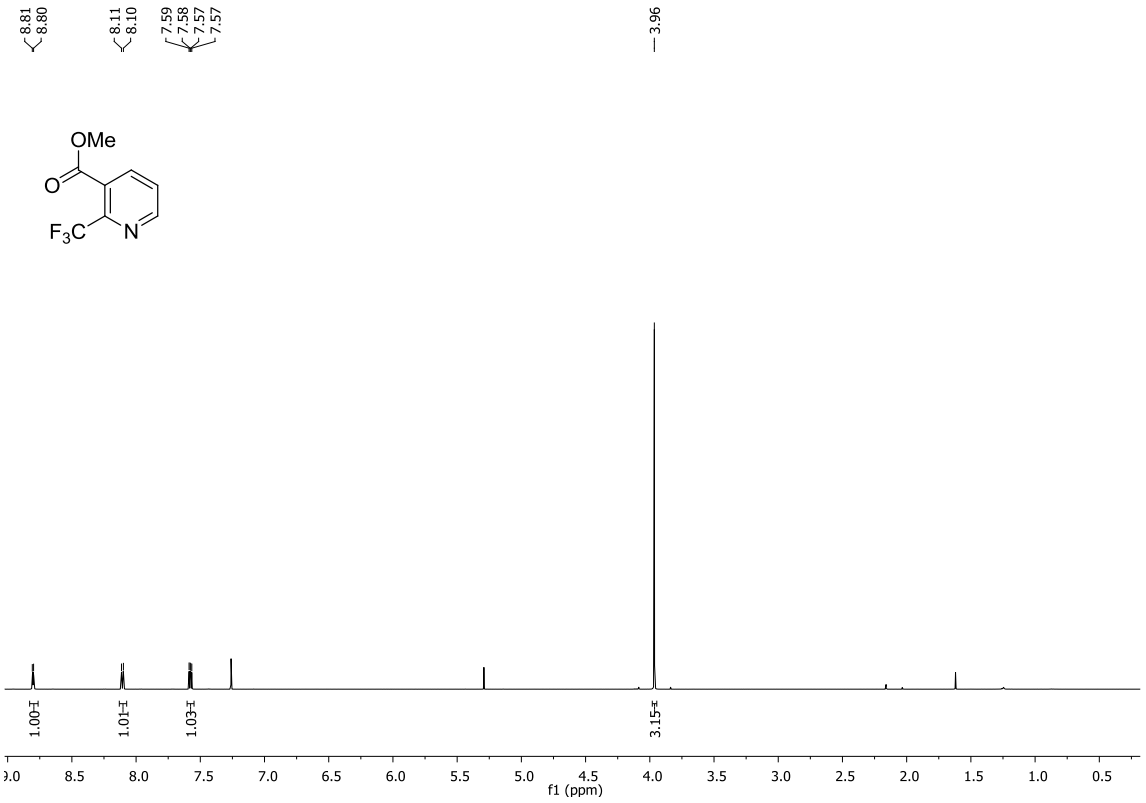
^{1}H NMR (600 MHz, $CDCl_3$) – **116a**



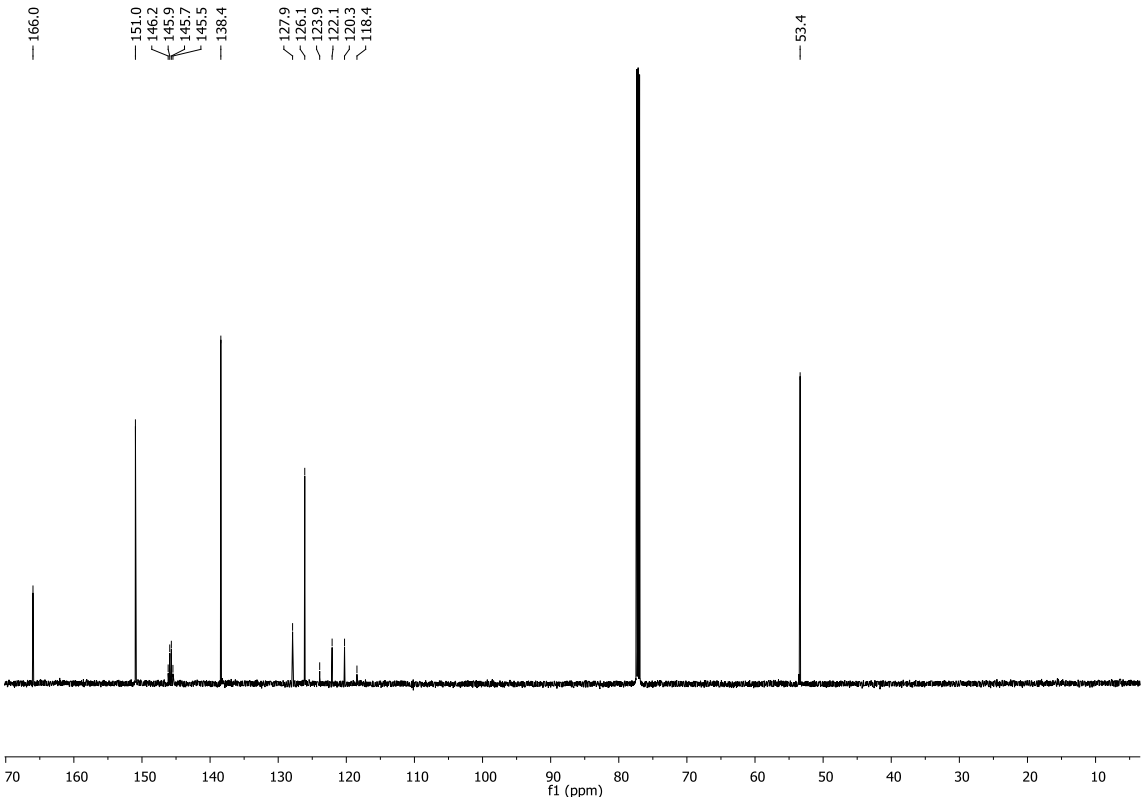
^{13}C NMR (101 MHz, $CDCl_3$) – **116a**



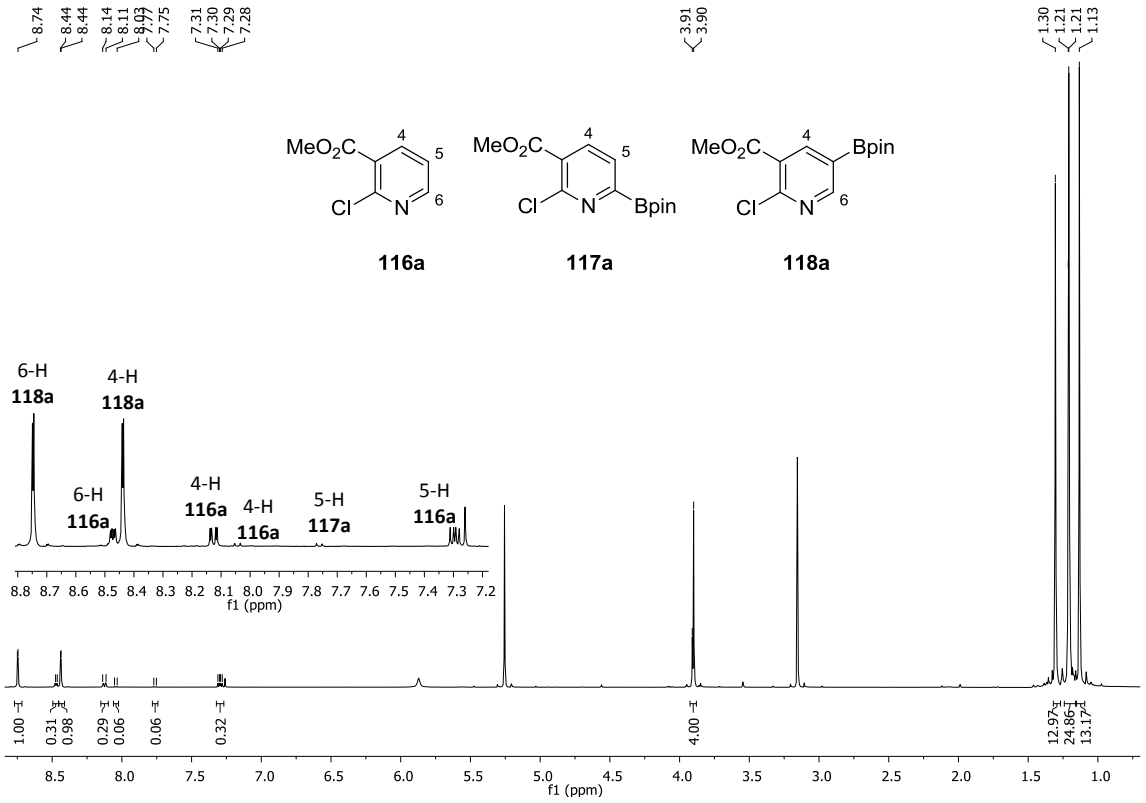
^{1}H NMR (600 MHz, $CDCl_3$) – **116b**



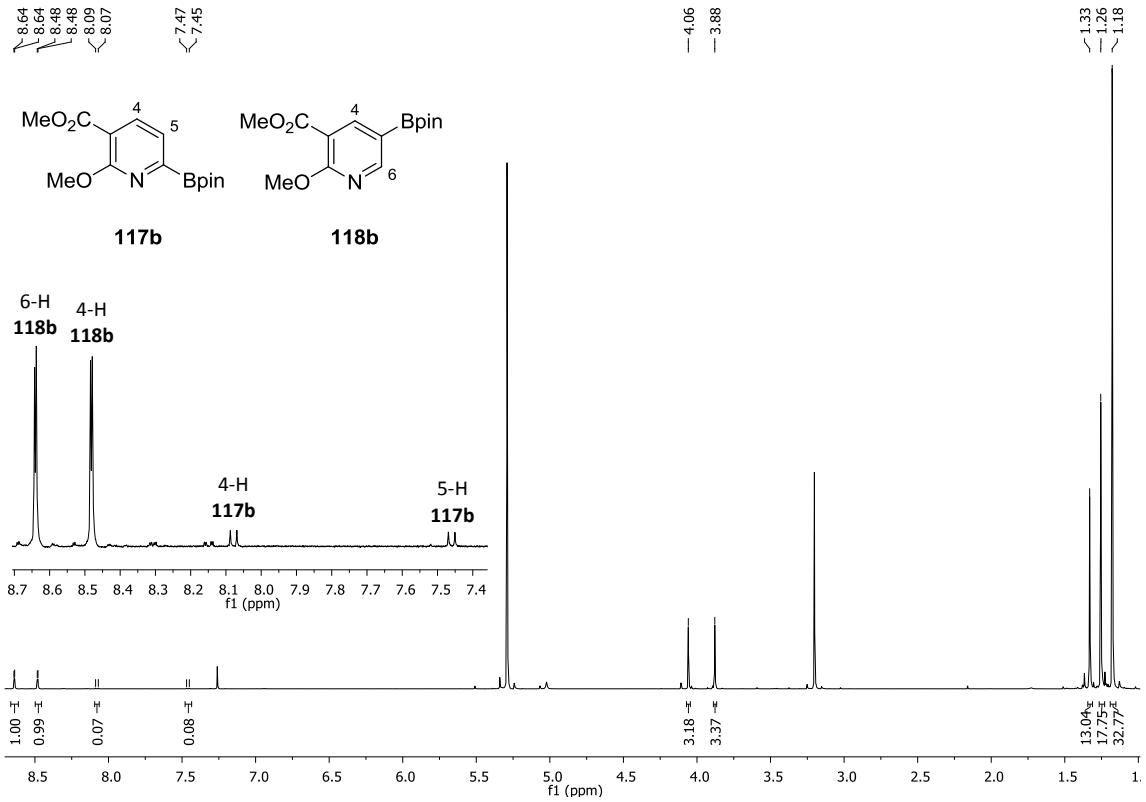
^{13}C NMR (101 MHz, $CDCl_3$) – **116b**



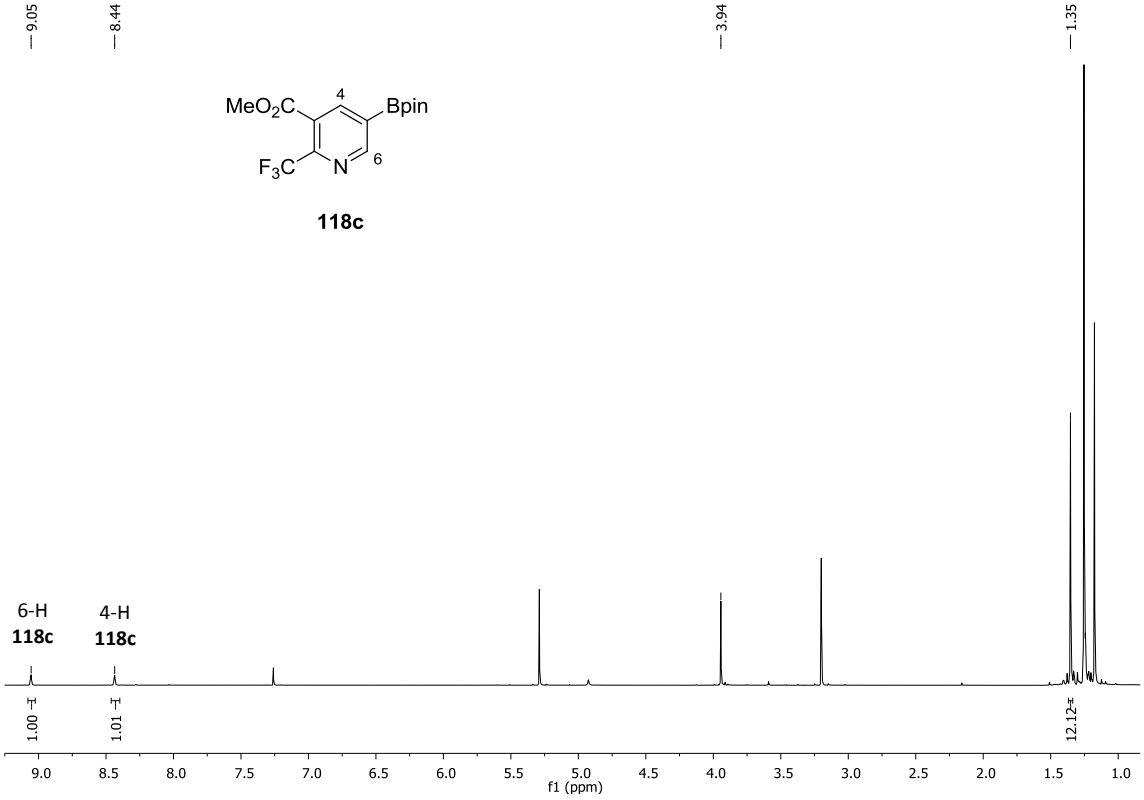
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of methyl 2-chloronicotinate (**116a**)



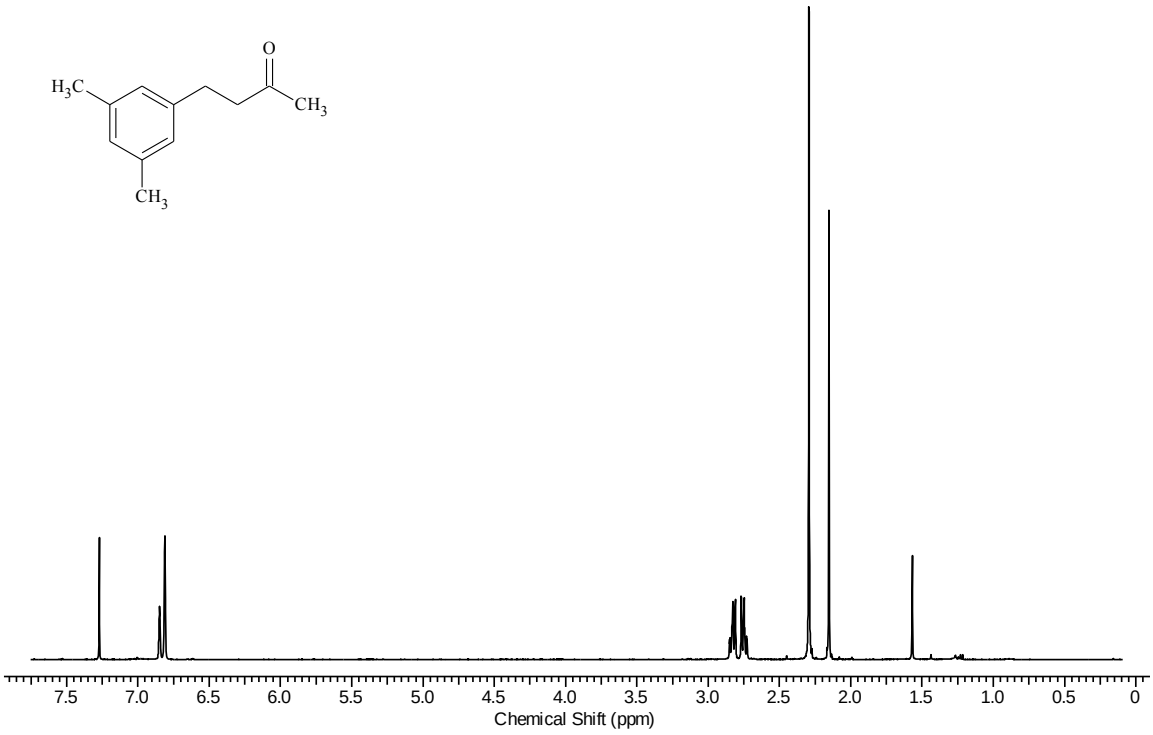
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of methyl 2-methoxynicotinate (**116b**)



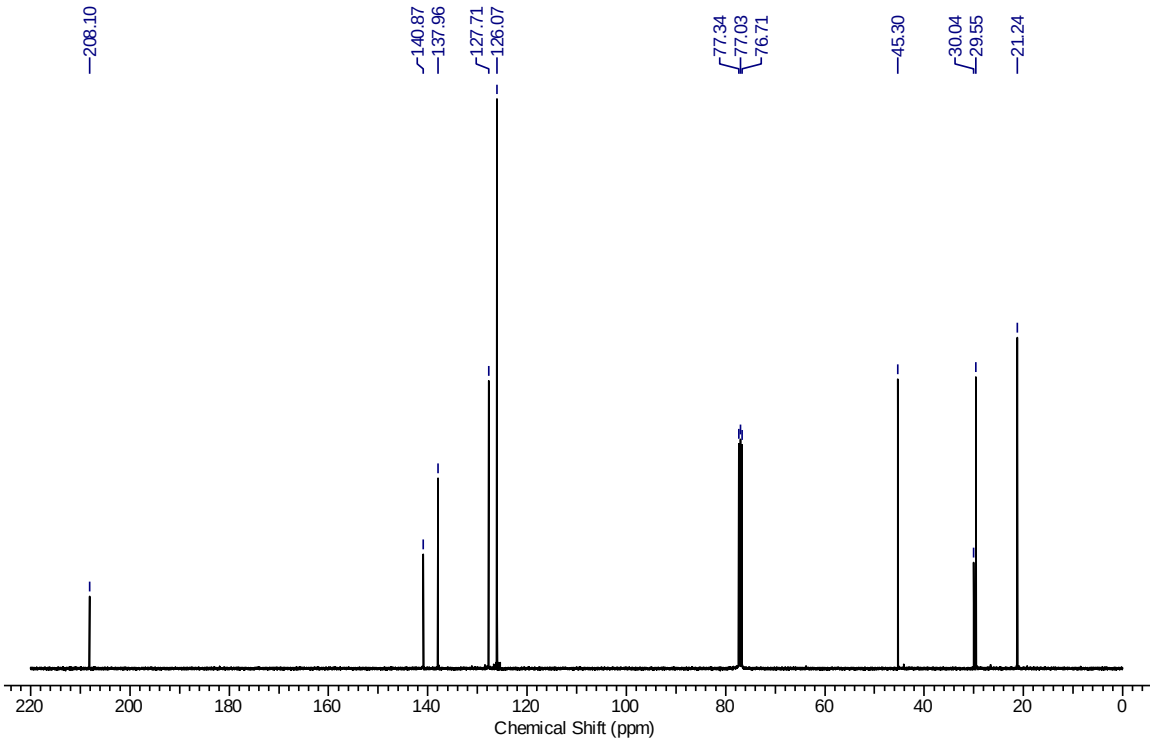
^{1}H NMR (400 MHz, $CDCl_3$) - Borylation of methyl 2-(trifluoromethyl)nicotinate (**116c**)



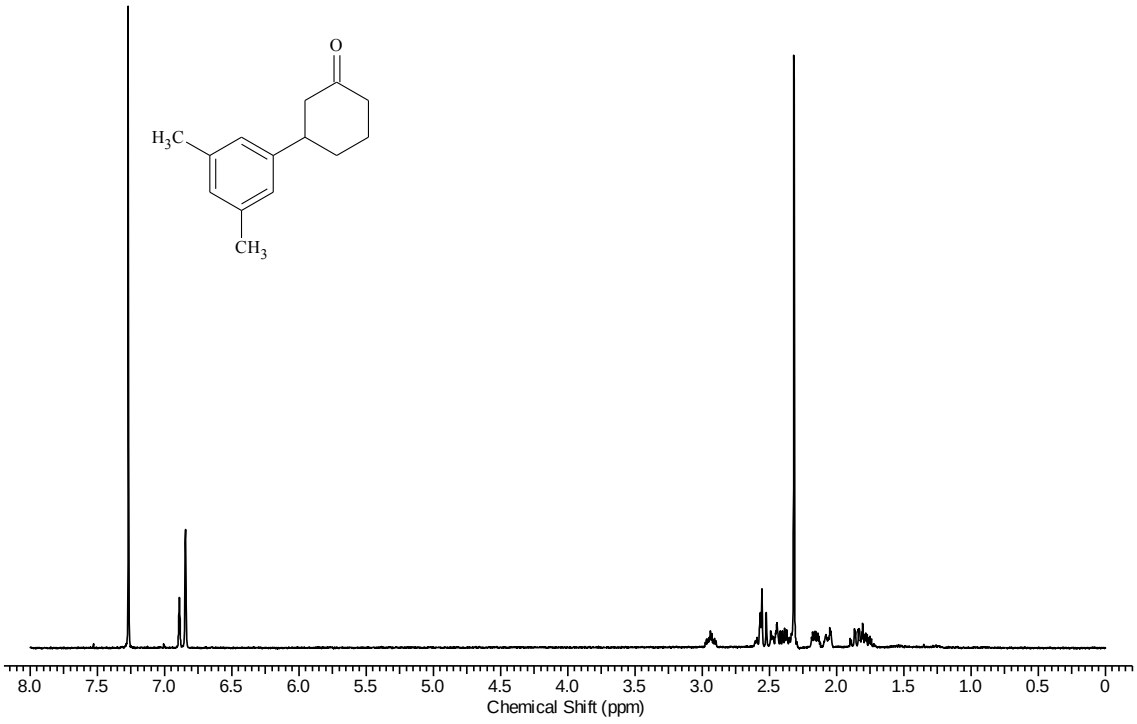
^{1}H NMR (400 MHz, $CDCl_3$) - **163**



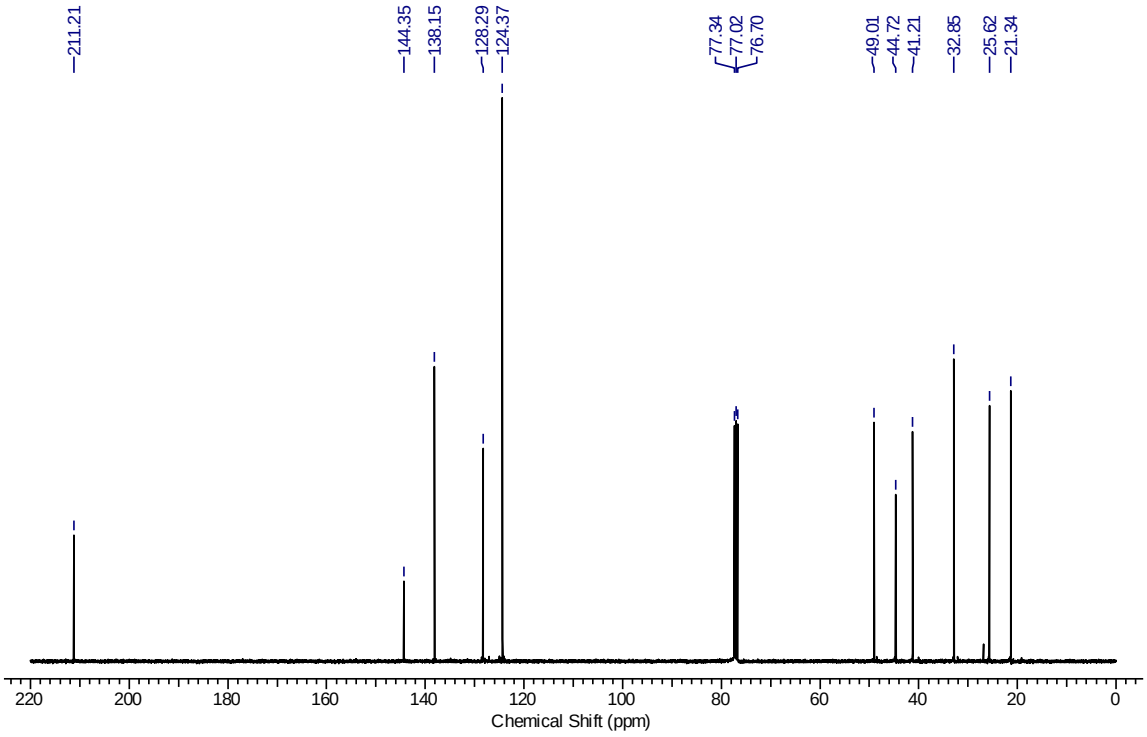
^{13}C NMR (101 MHz, $CDCl_3$) - **163**



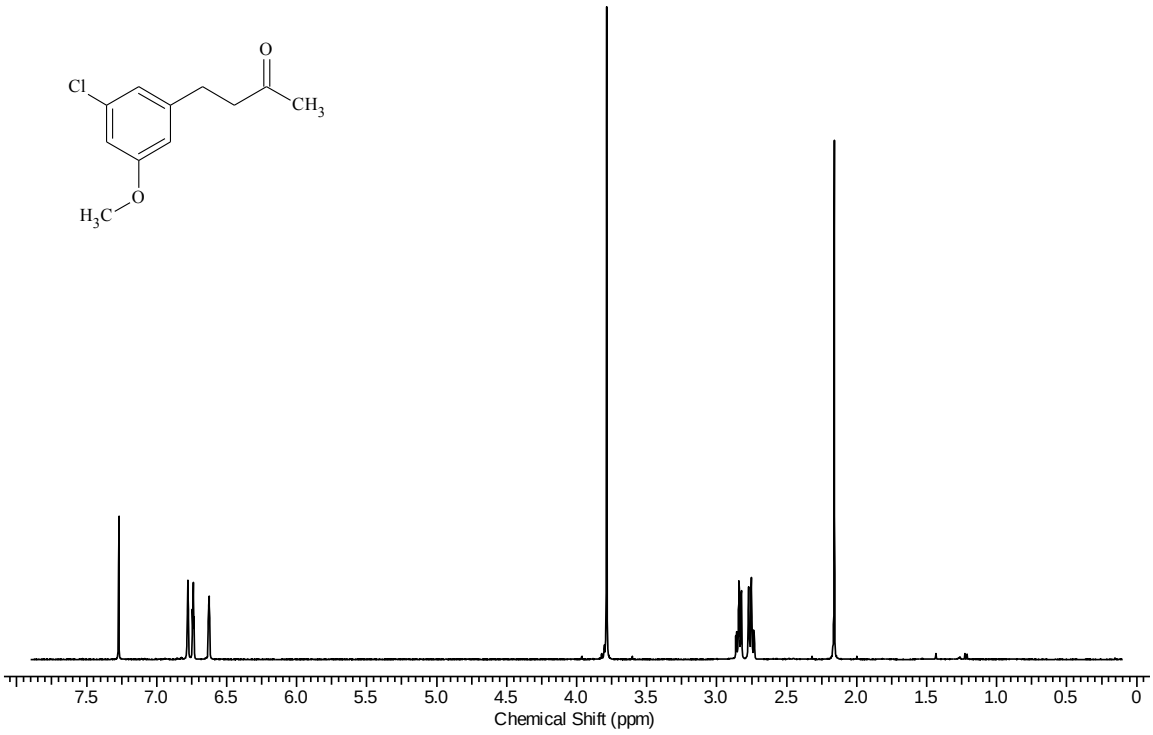
^{1}H NMR (400 MHz, $CDCl_3$) - **194**



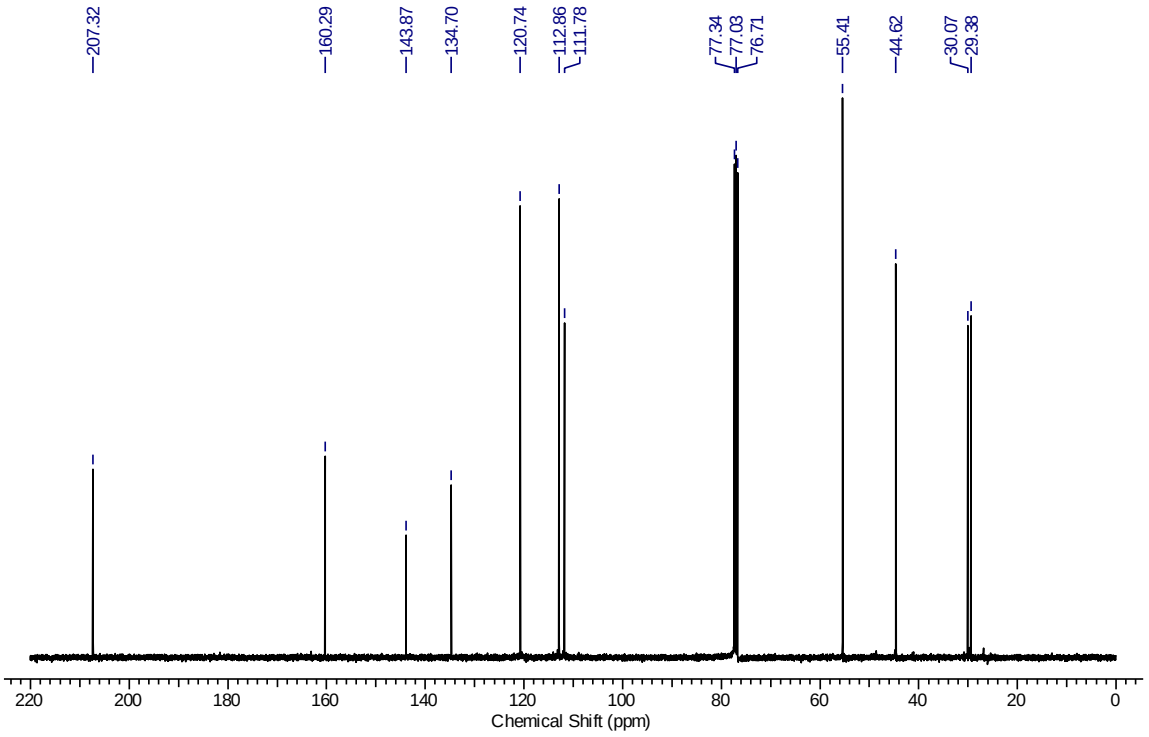
^{13}C NMR (101 MHz, $CDCl_3$) - **194**



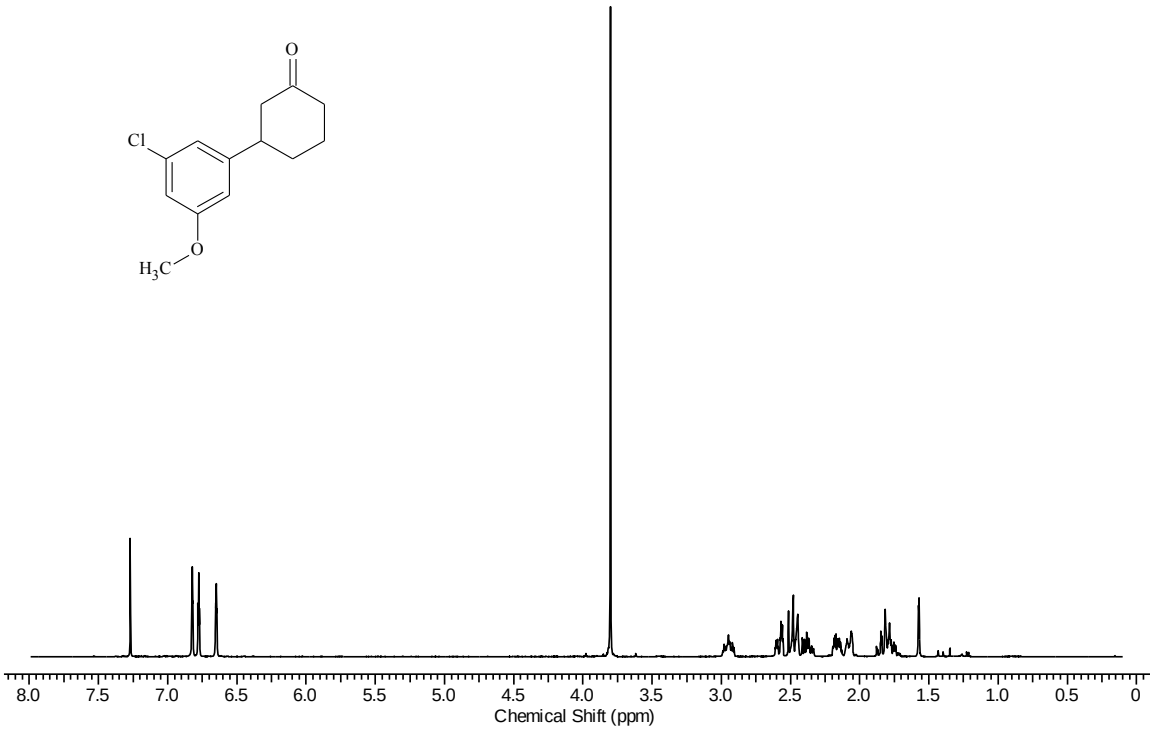
^{1}H NMR (400 MHz, $CDCl_3$) - **164**



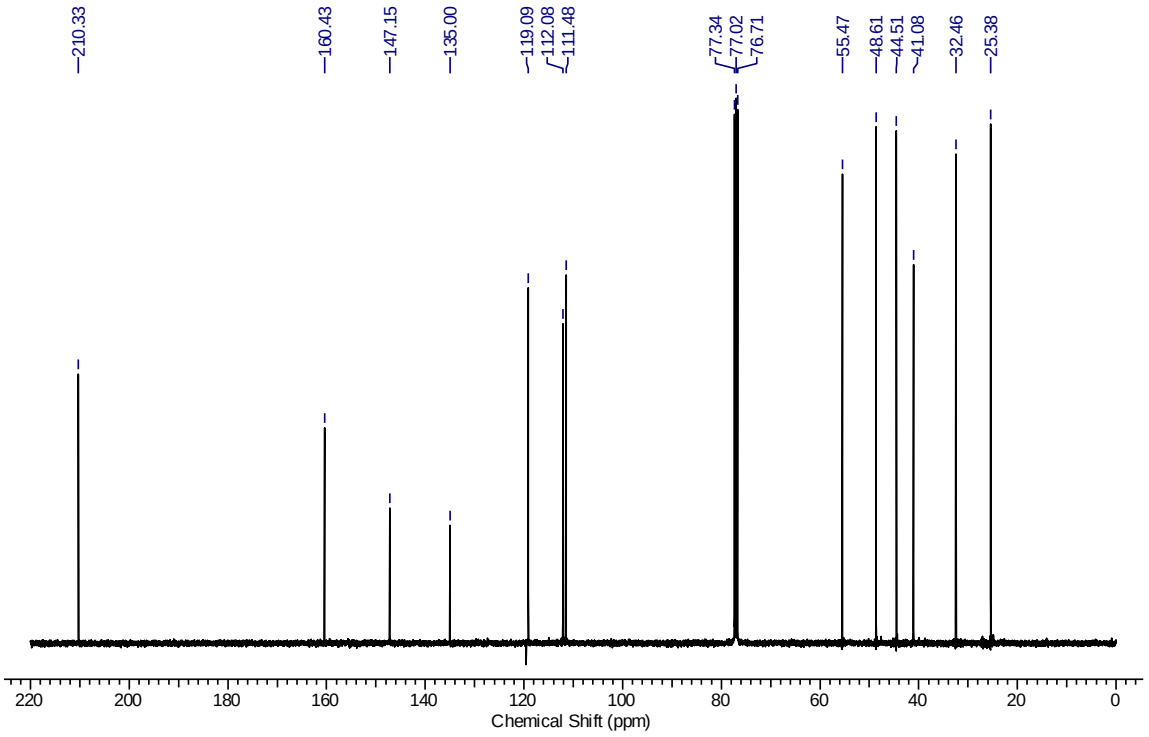
^{13}C NMR (101 MHz, $CDCl_3$) - **164**



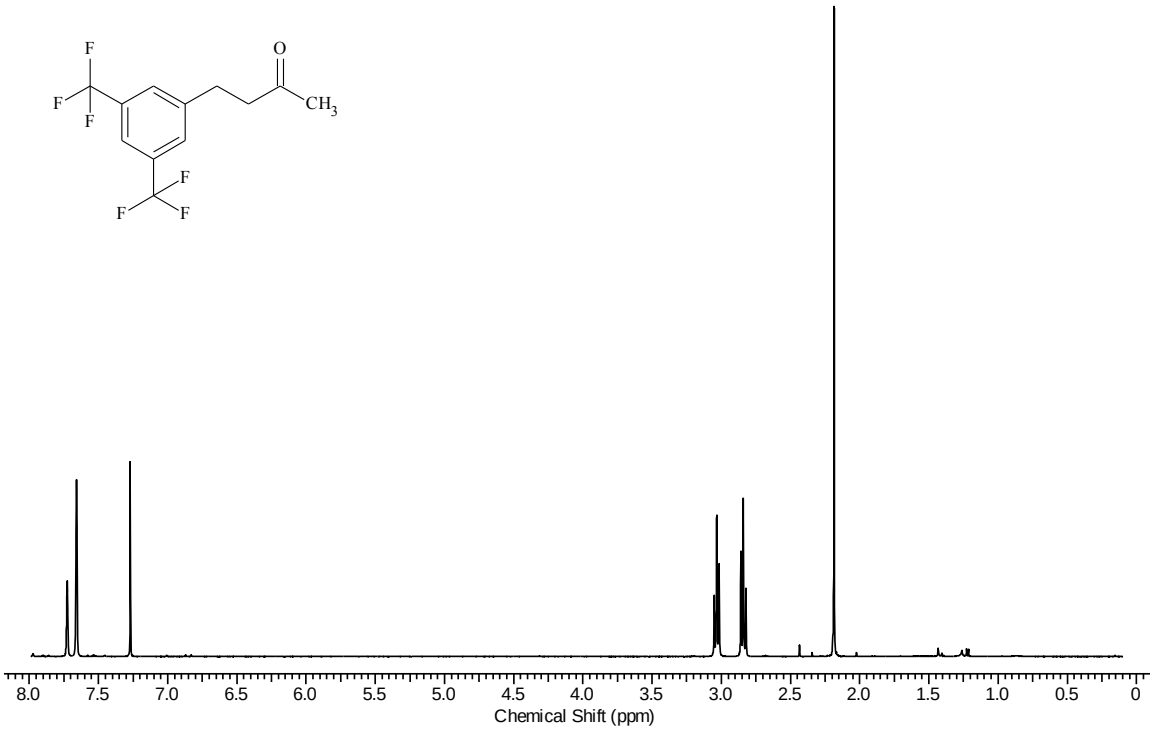
^{1}H NMR (400 MHz, $CDCl_3$) - **195**



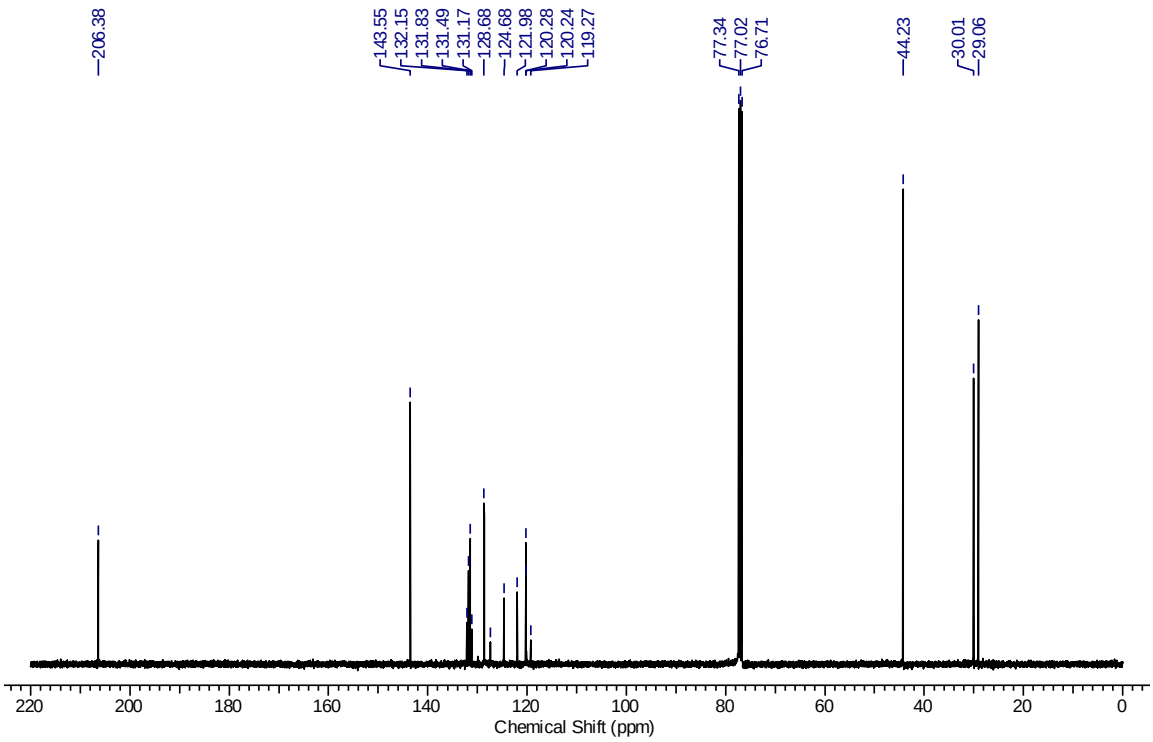
^{13}C NMR (101 MHz, $CDCl_3$) - **195**



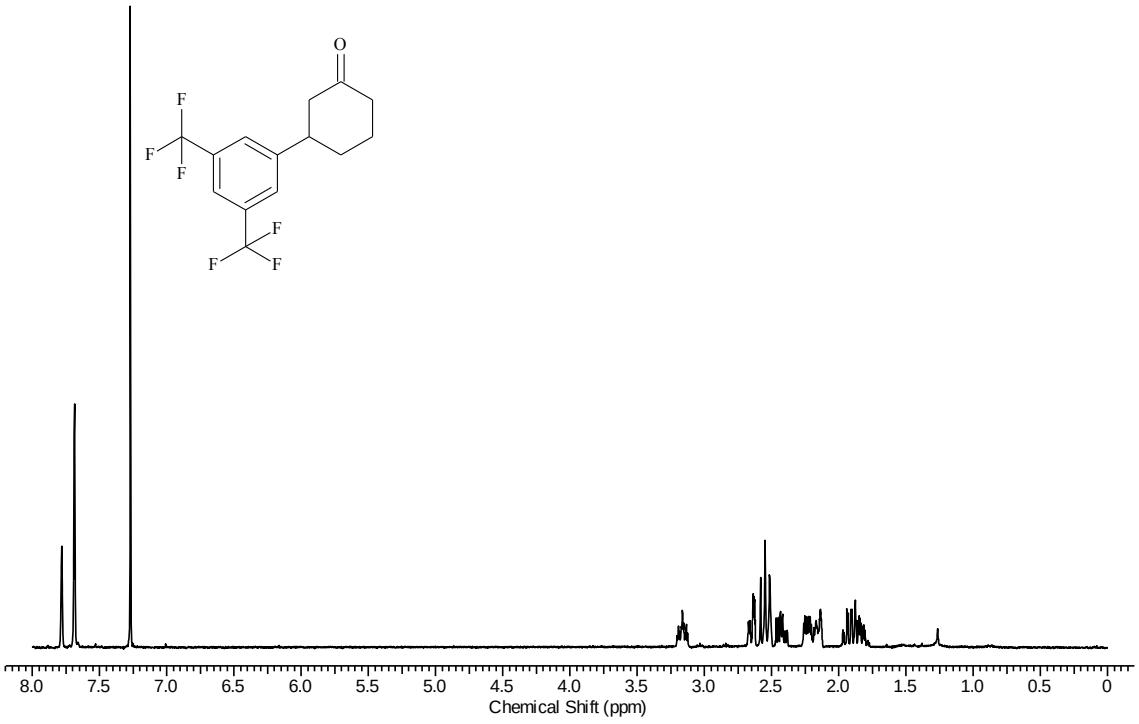
^{1}H NMR (400 MHz, $CDCl_3$) - **166**



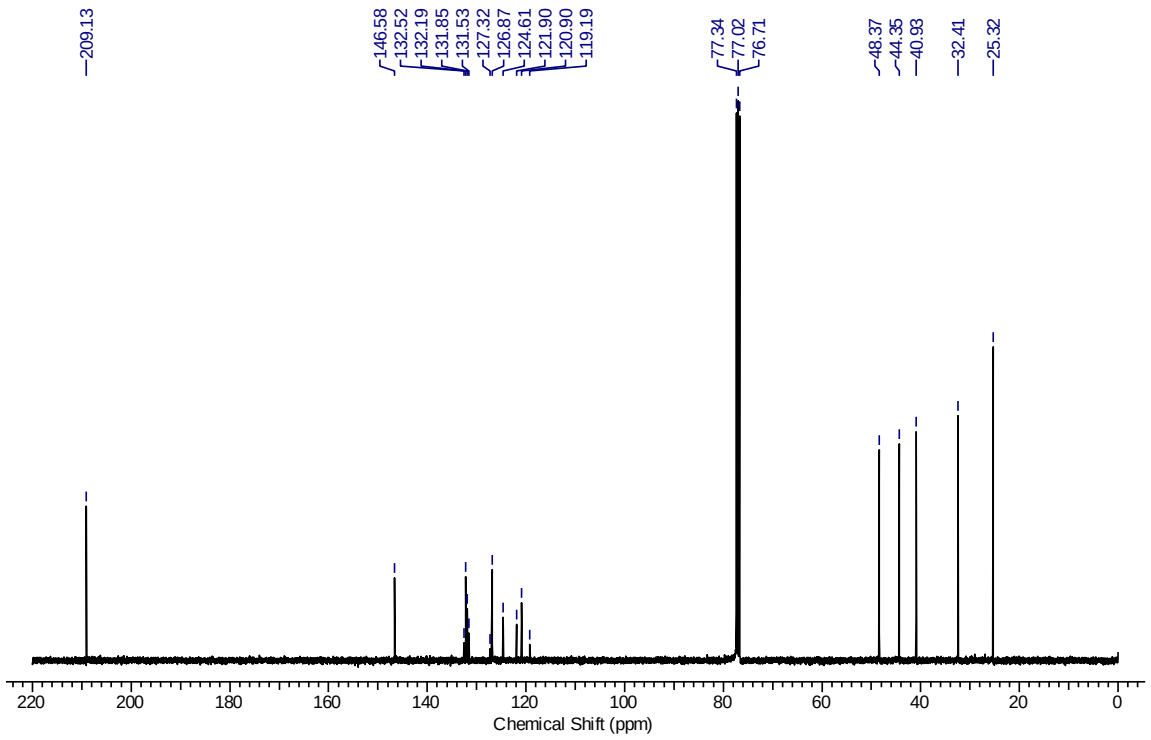
^{13}C NMR (101 MHz, $CDCl_3$) - **166**



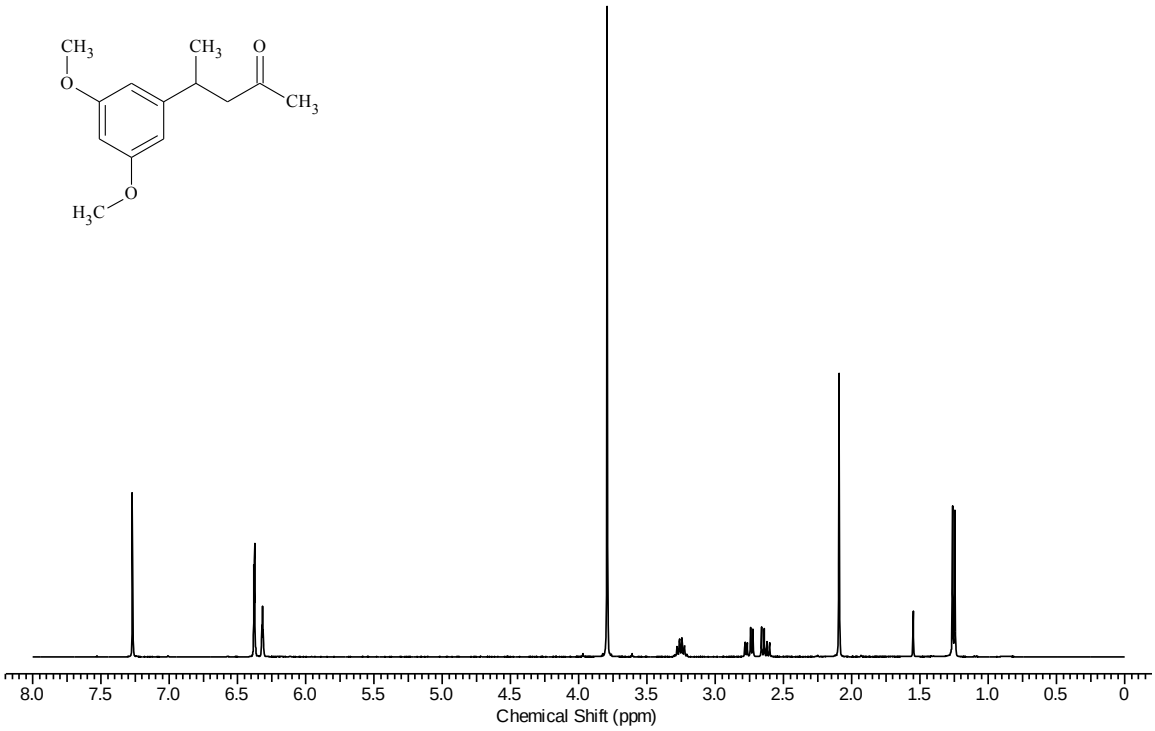
^{1}H NMR (400 MHz, $CDCl_3$) - **196**



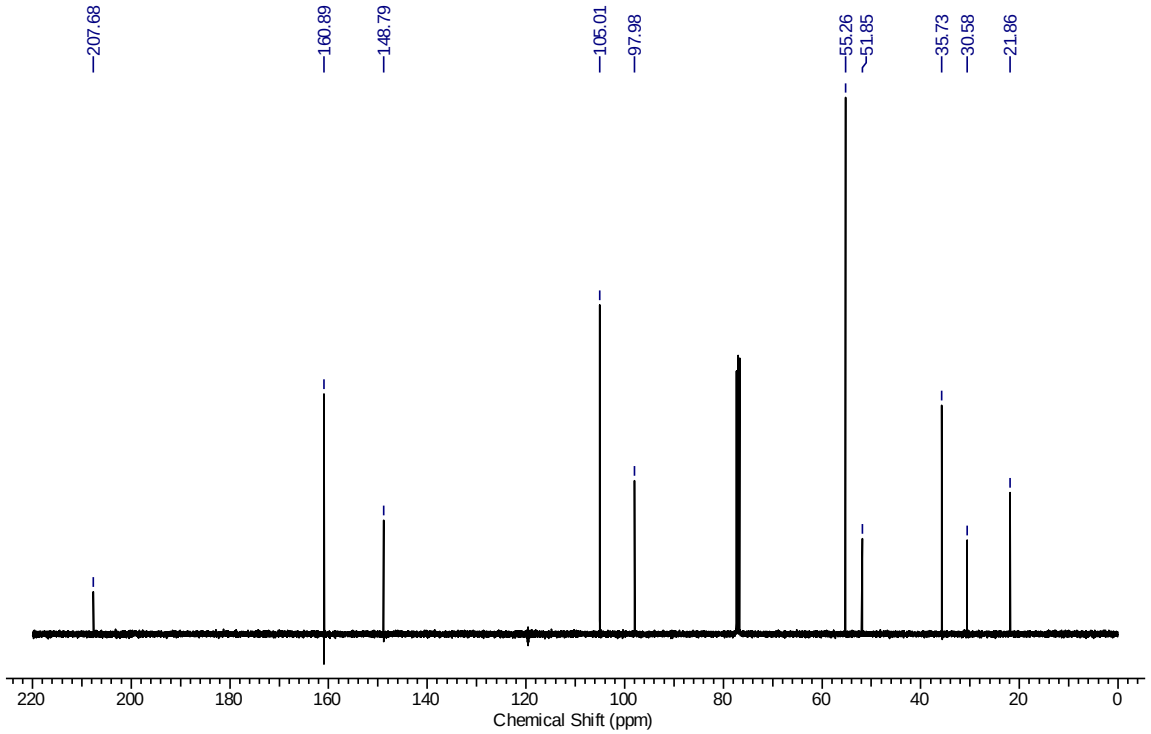
^{13}C NMR (101 MHz, $CDCl_3$) - **196**



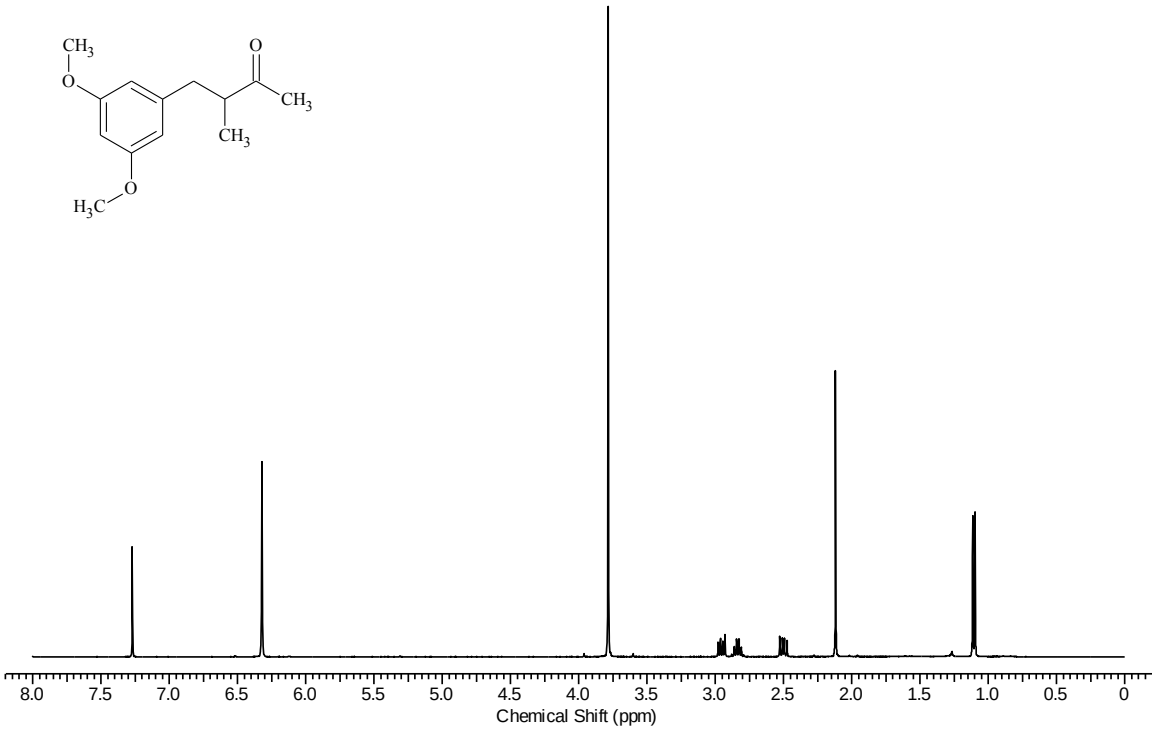
^{1}H NMR (400 MHz, $CDCl_3$) - **197**



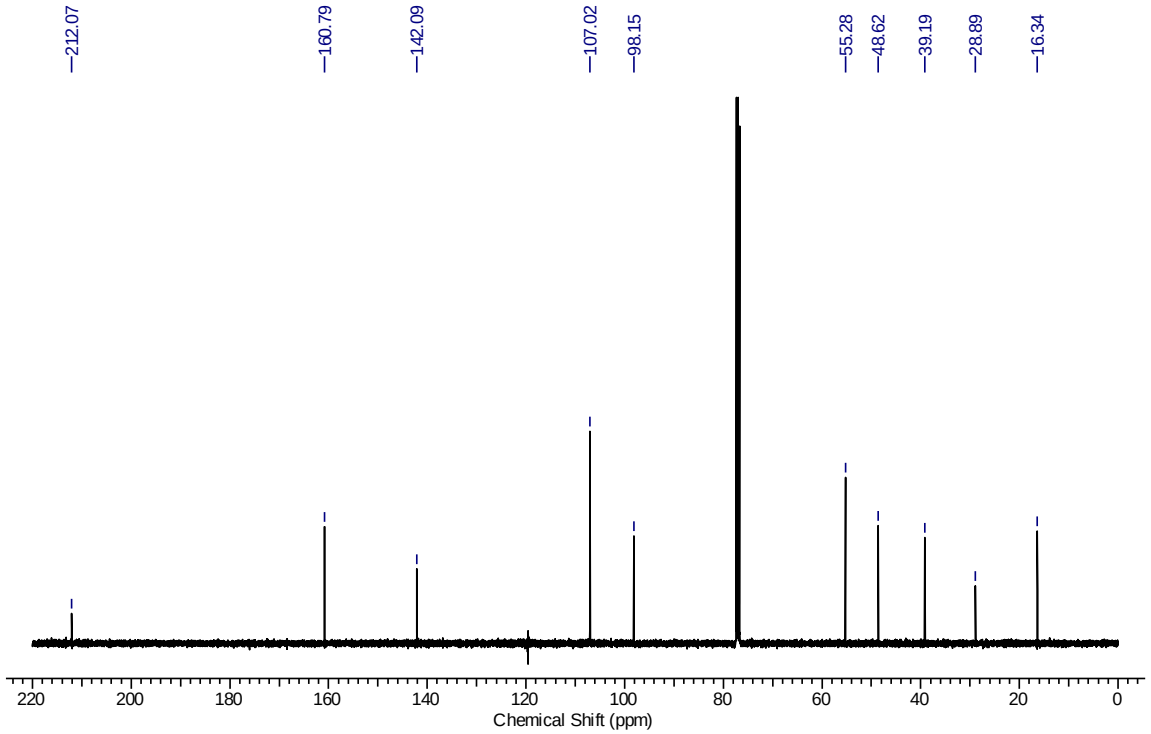
^{13}C NMR (101 MHz, $CDCl_3$) - **197**



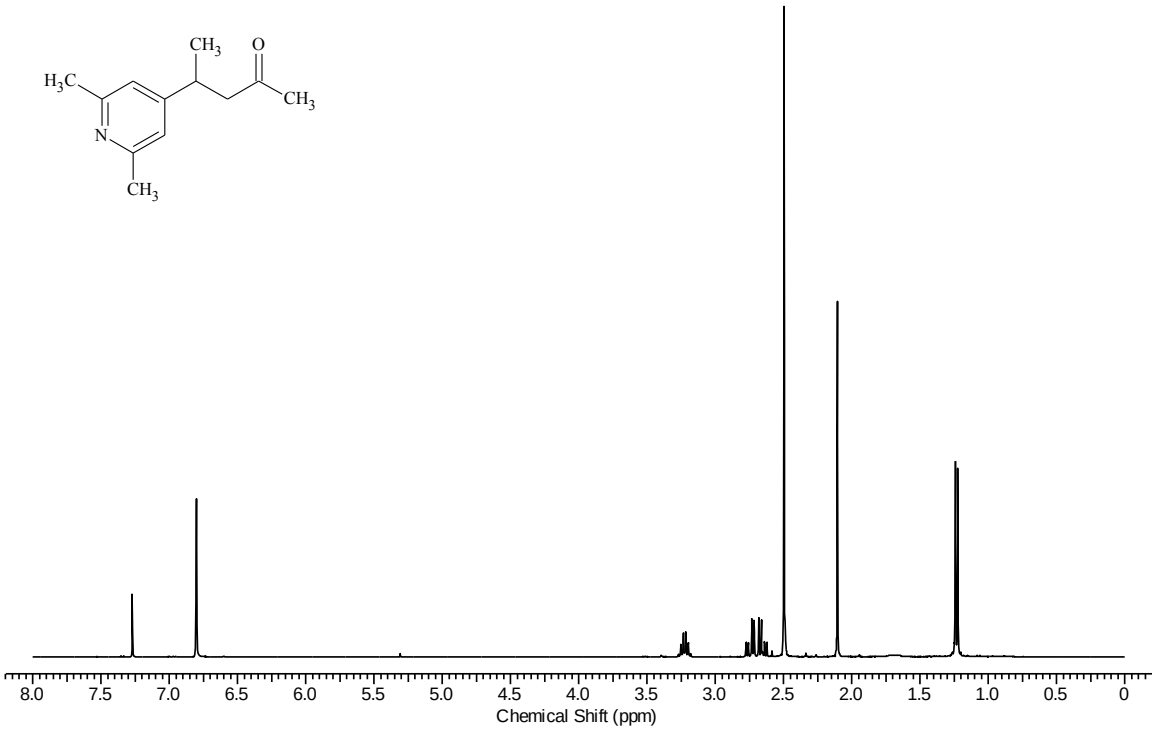
^{1}H NMR (400 MHz, $CDCl_3$) - **198**



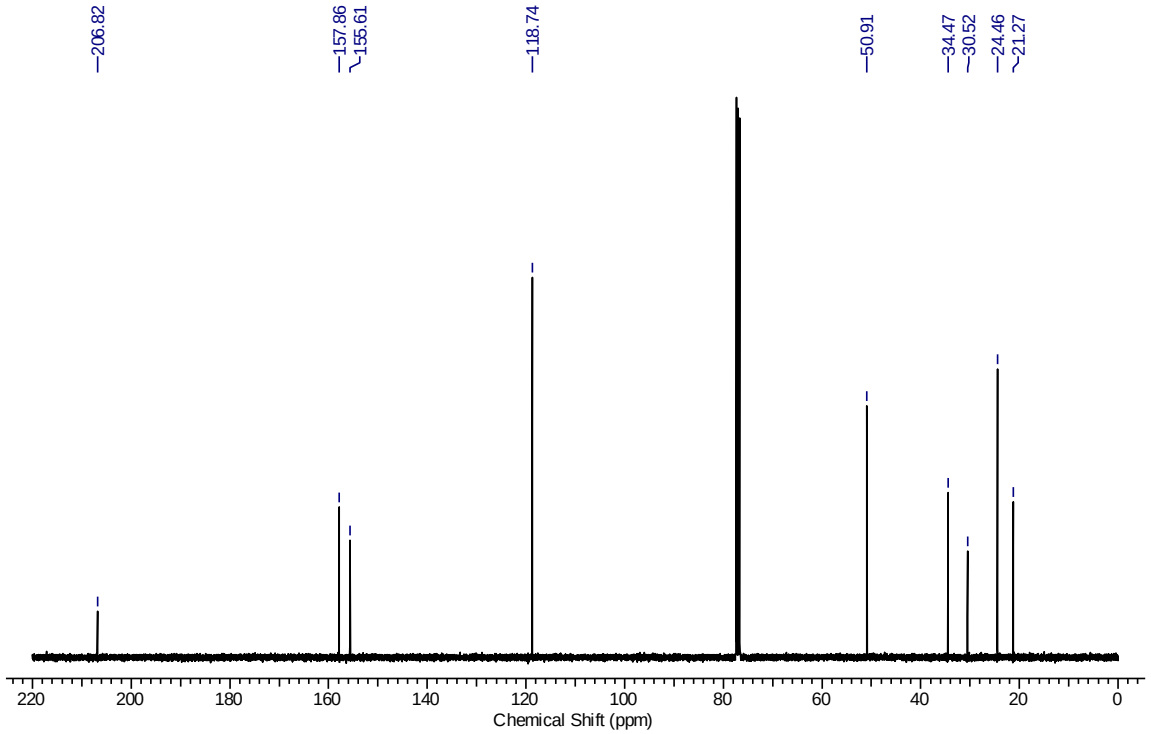
^{13}C NMR (101 MHz, $CDCl_3$) - **198**



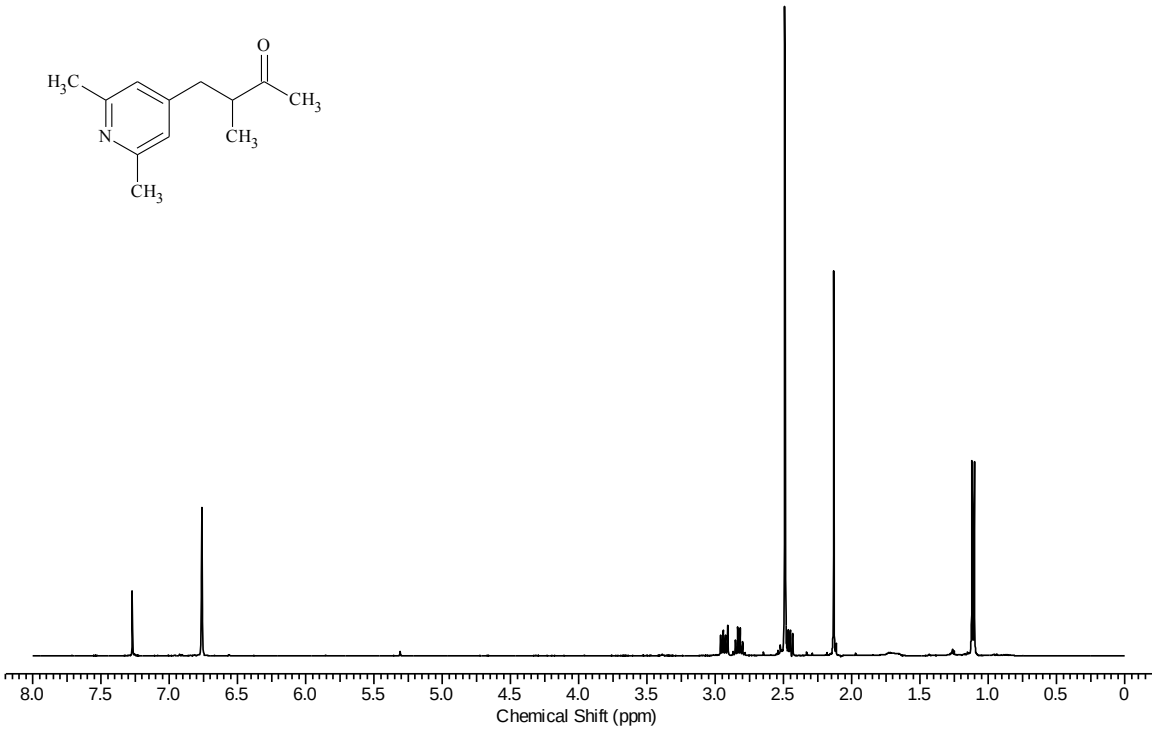
^{1}H NMR (400 MHz, $CDCl_3$) - **199**



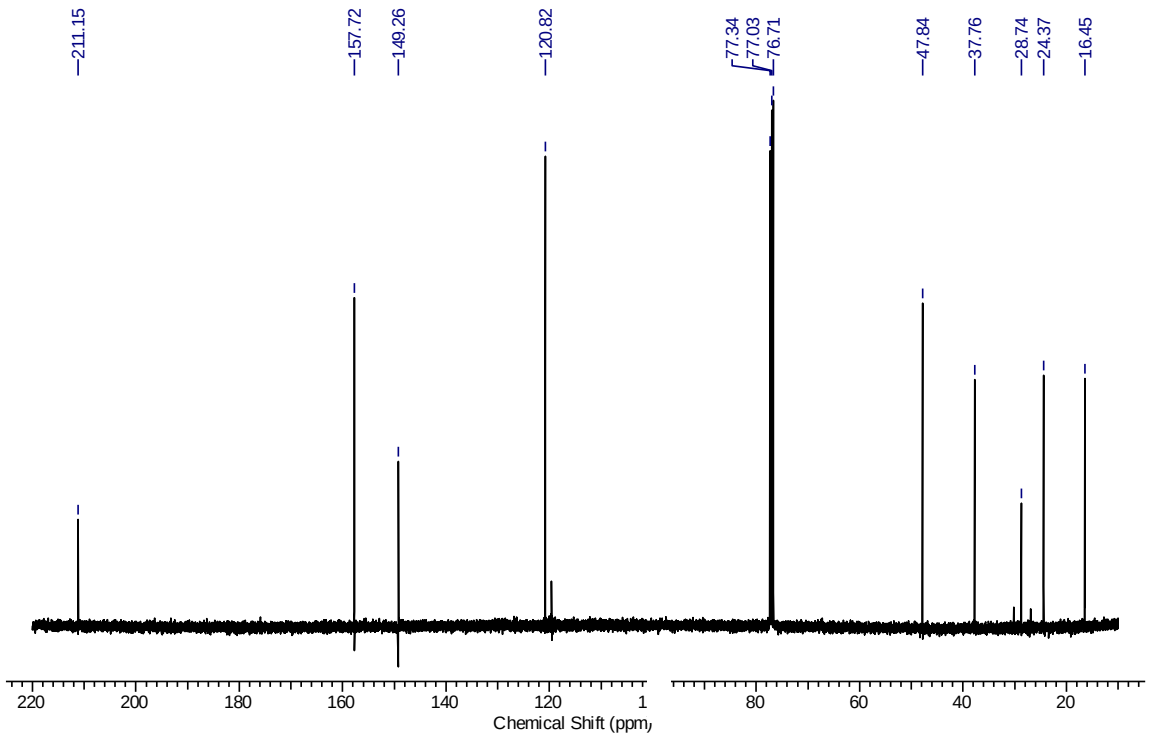
^{13}C NMR (101 MHz, $CDCl_3$) - **199**



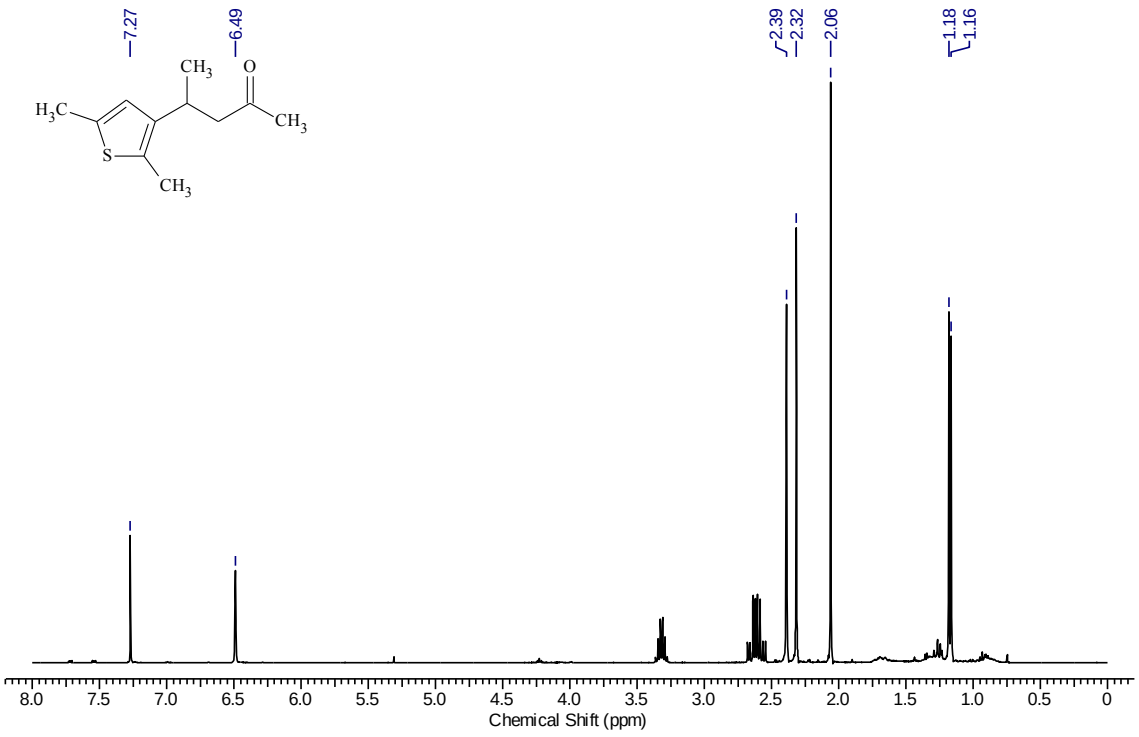
^{1}H NMR (400 MHz, $CDCl_3$) - **200**



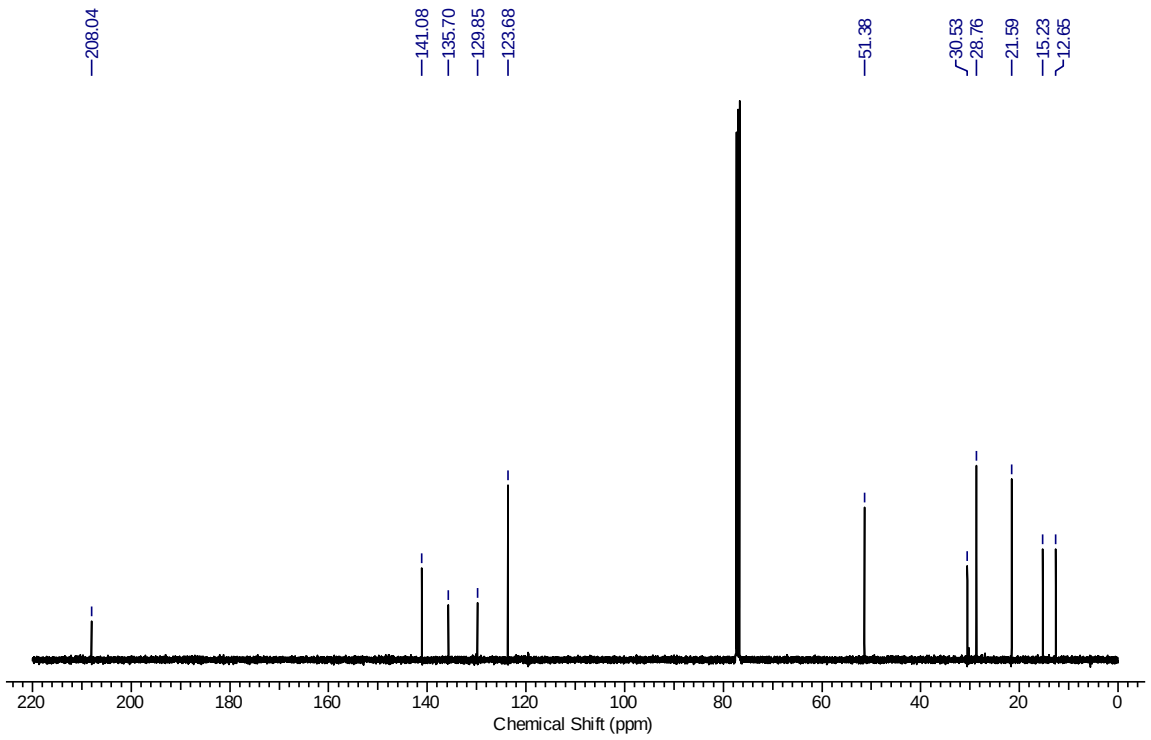
^{13}C NMR (101 MHz, $CDCl_3$) - **200**



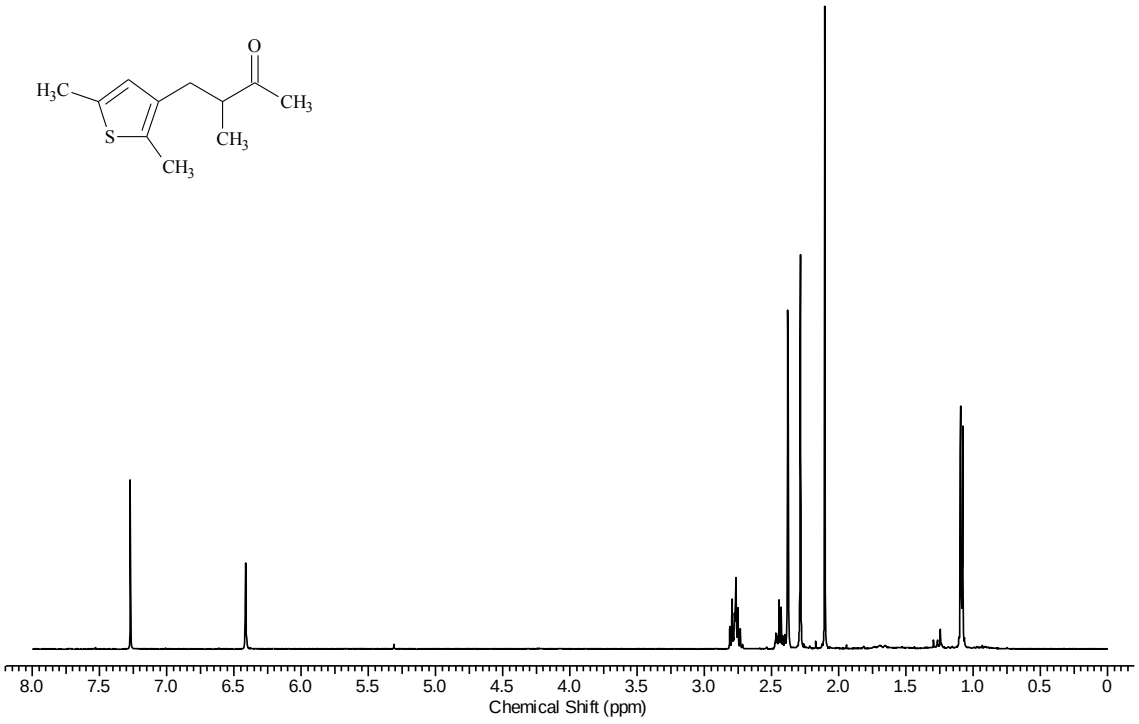
^{1}H NMR (400 MHz, $CDCl_3$) - **201**



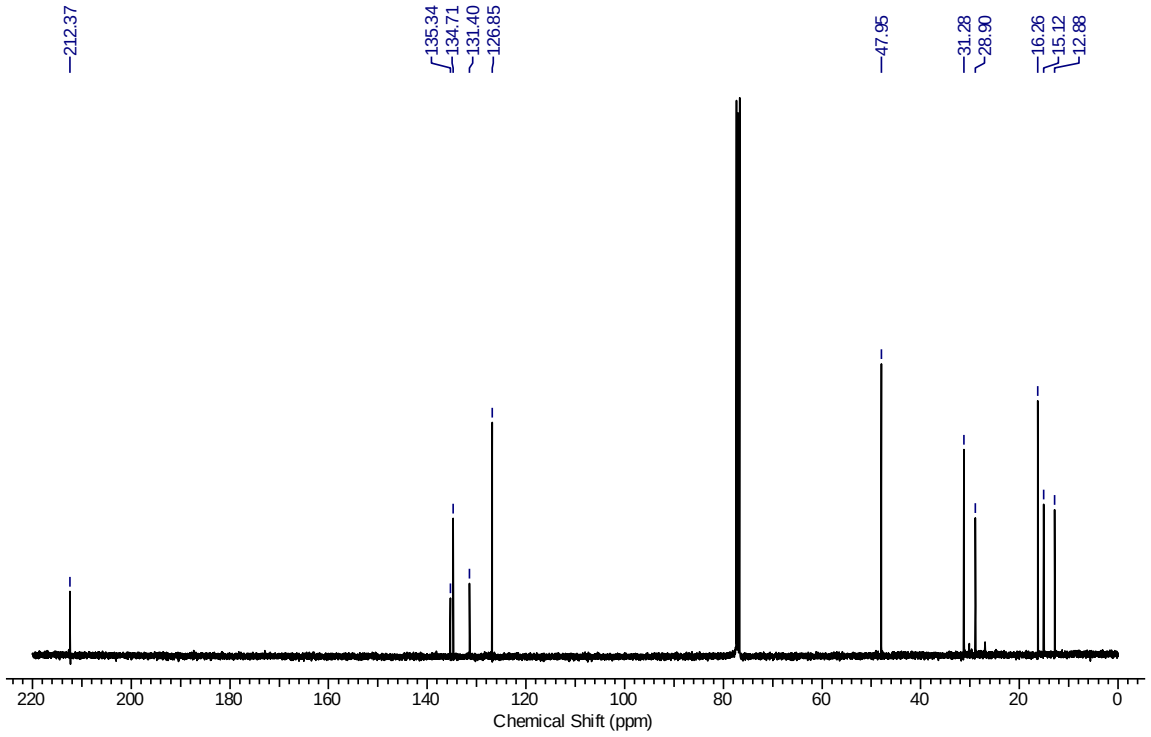
^{13}C NMR (101 MHz, $CDCl_3$) - **201**



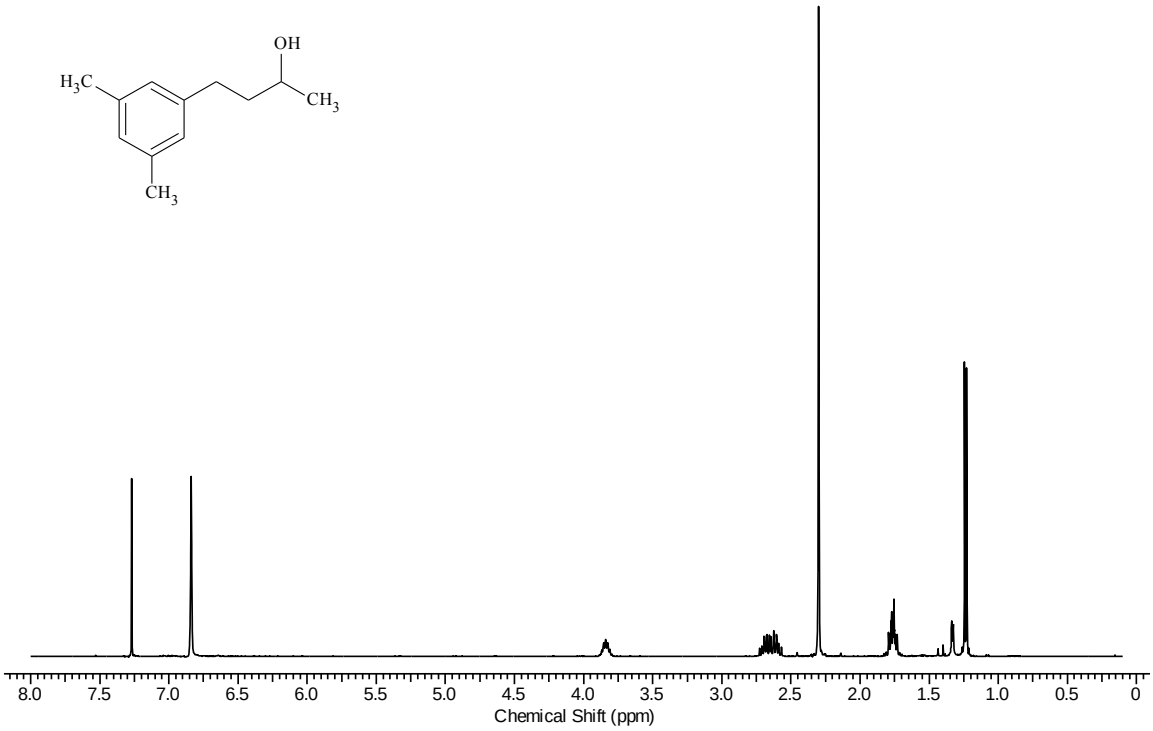
^{1}H NMR (400 MHz, $CDCl_3$) - **202**



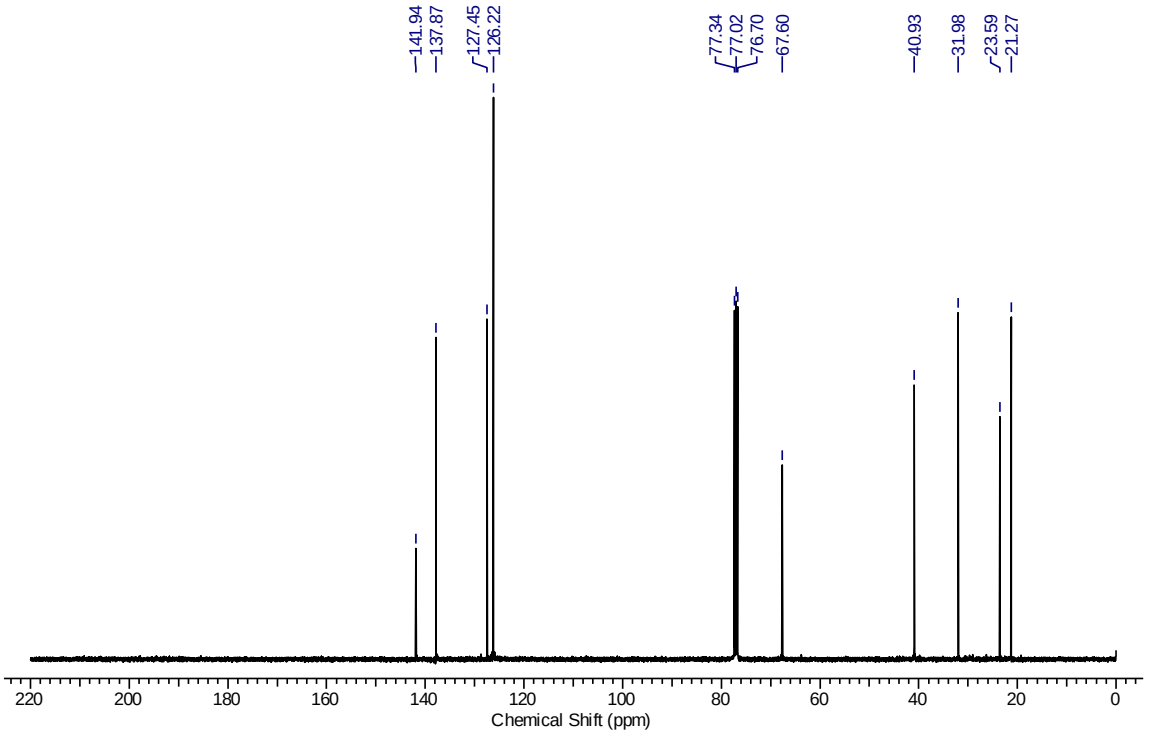
^{13}C NMR (101 MHz, $CDCl_3$) - **202**



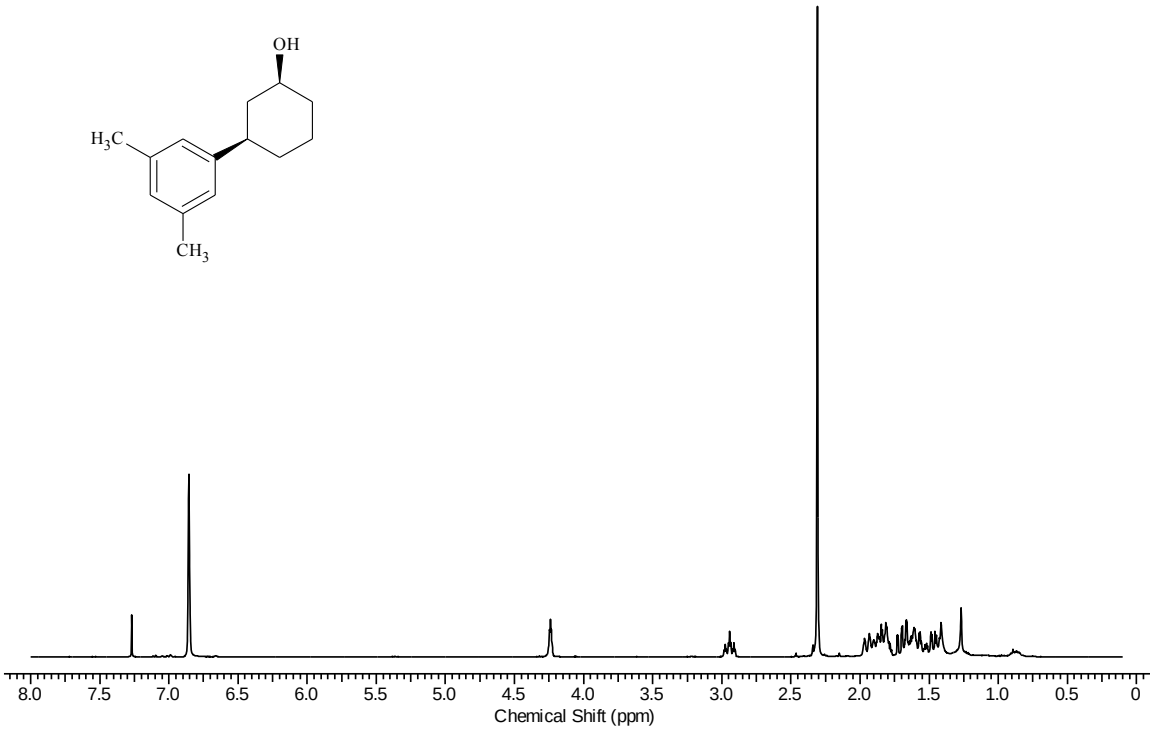
^{1}H NMR (400 MHz, $CDCl_3$) - **186**



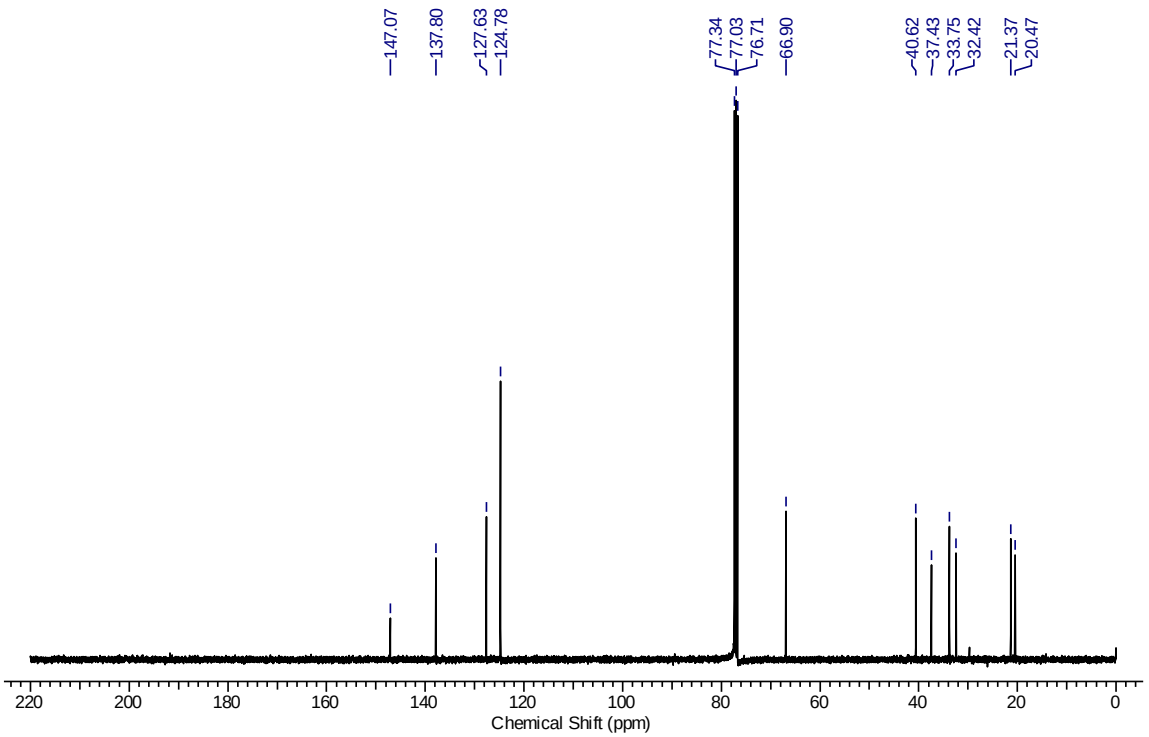
^{13}C NMR (101 MHz, $CDCl_3$) - **186**



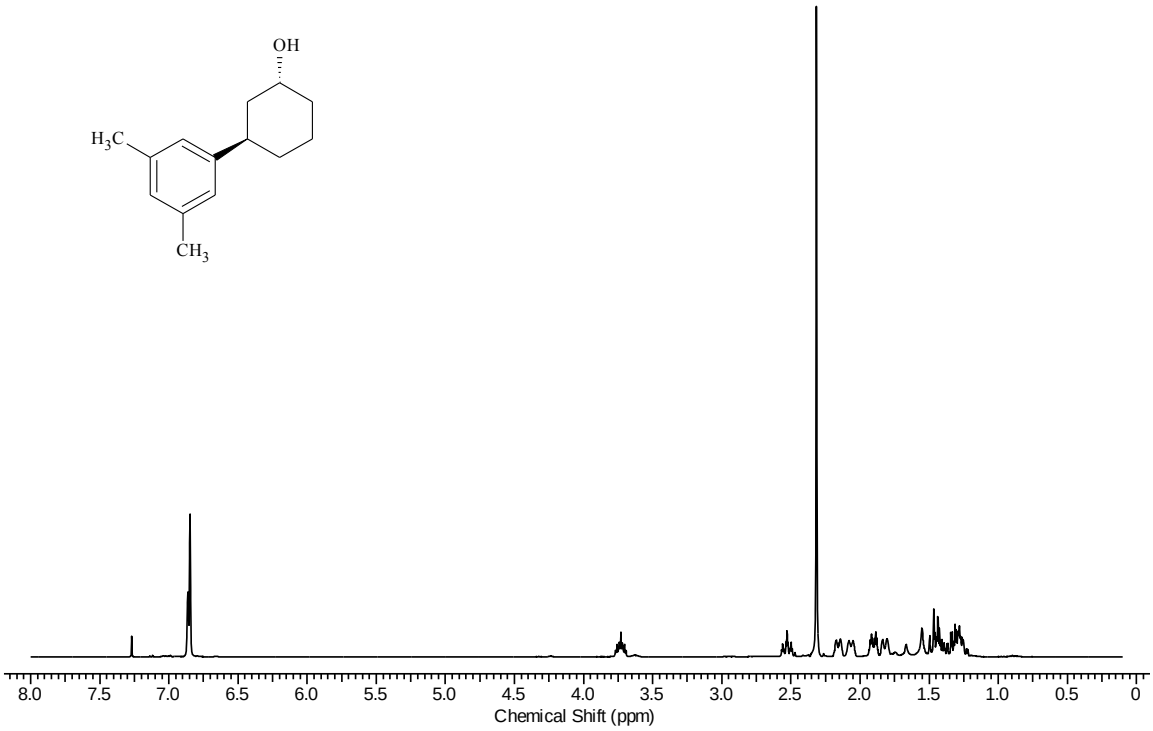
^{1}H NMR (400 MHz, $CDCl_3$) – *syn*-**203**



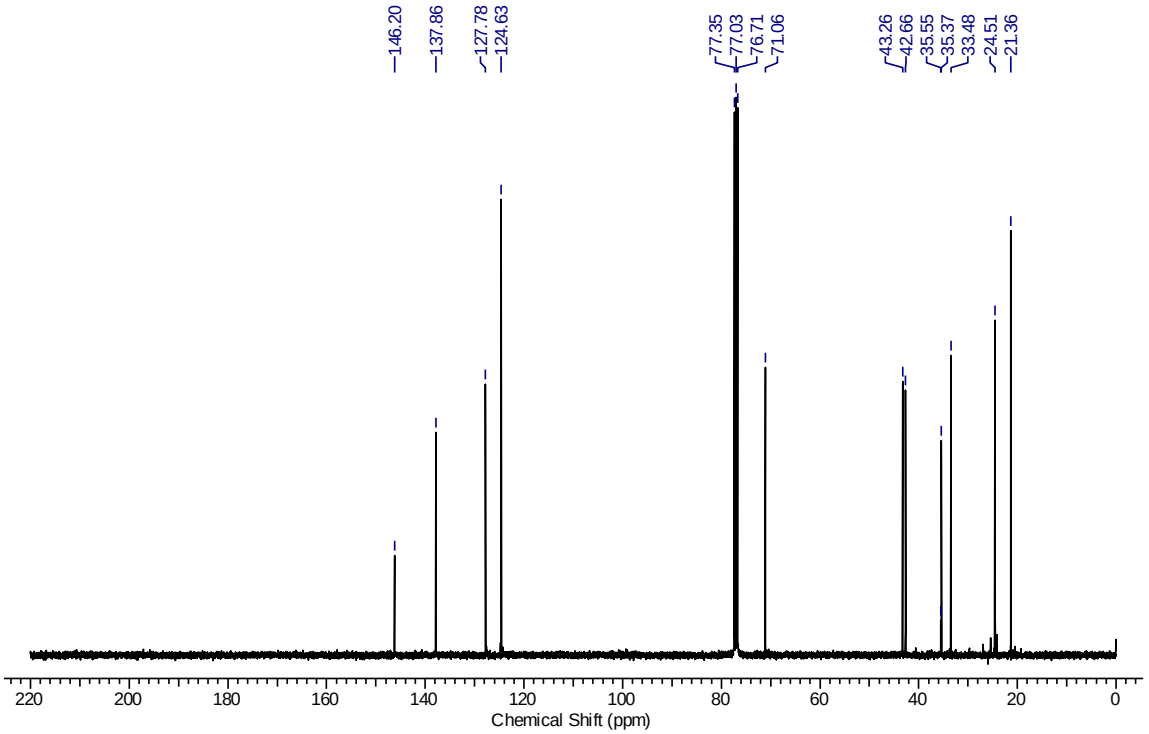
^{13}C NMR (101 MHz, $CDCl_3$) – *syn*-**203**



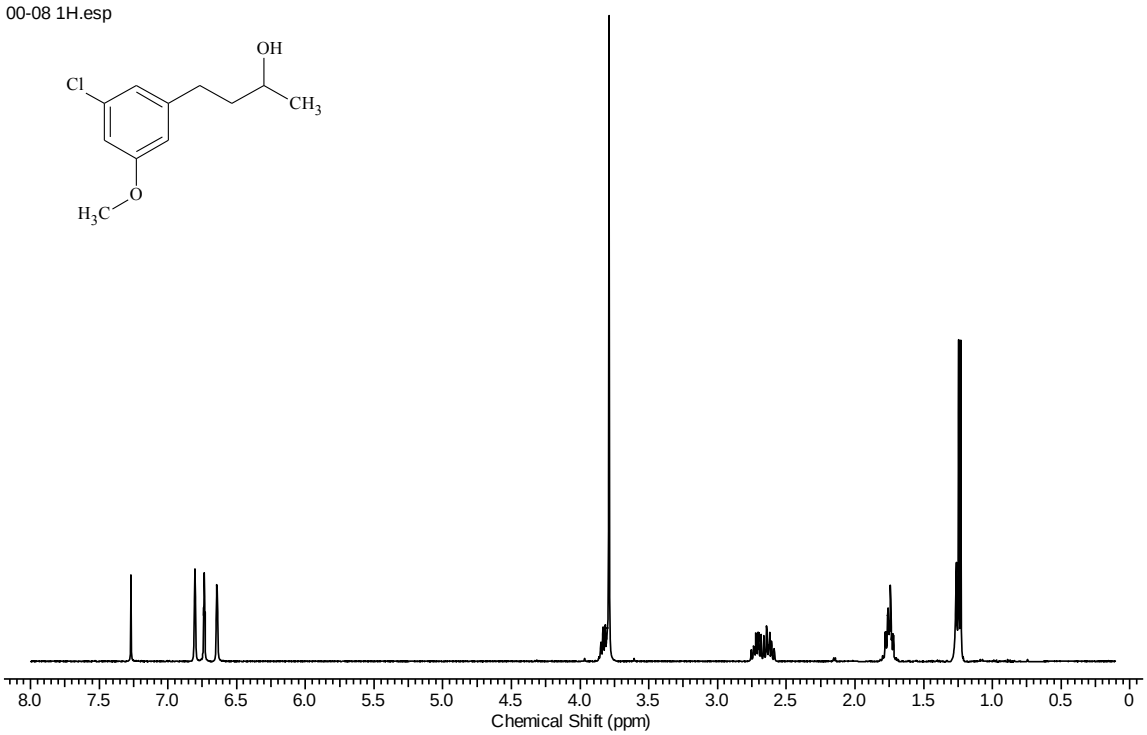
^{1}H NMR (400 MHz, $CDCl_3$) – *anti*-**203**



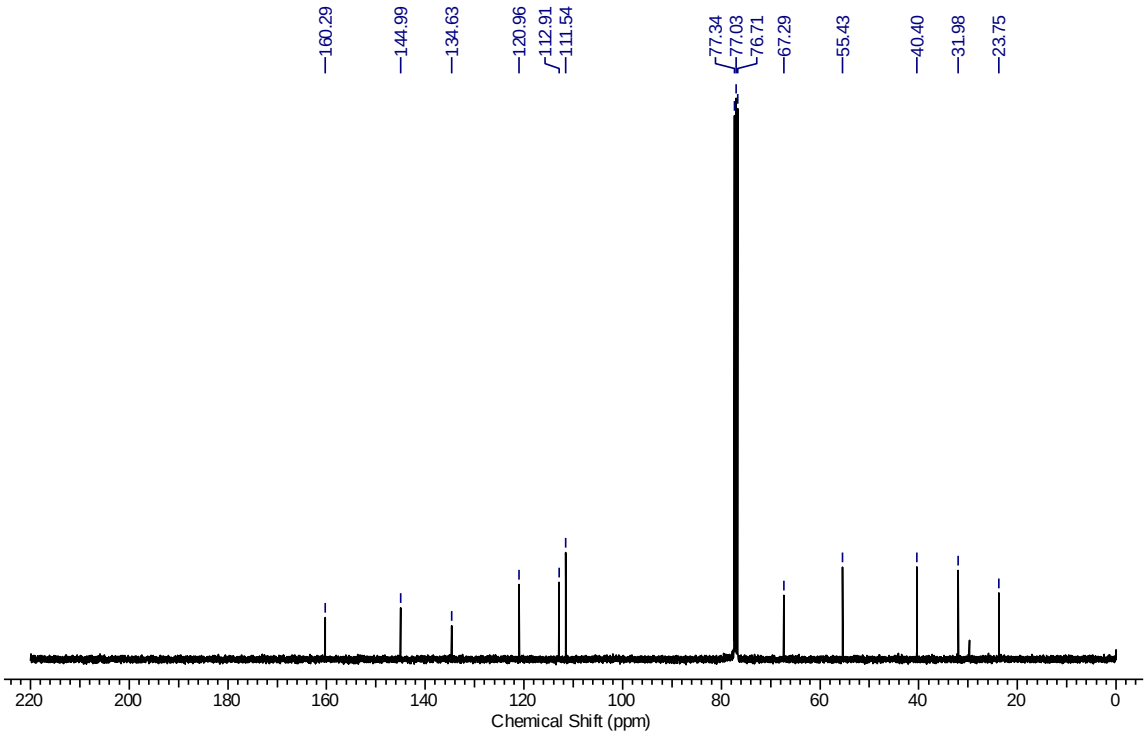
^{13}C NMR (101 MHz, $CDCl_3$) – *anti*-**203**



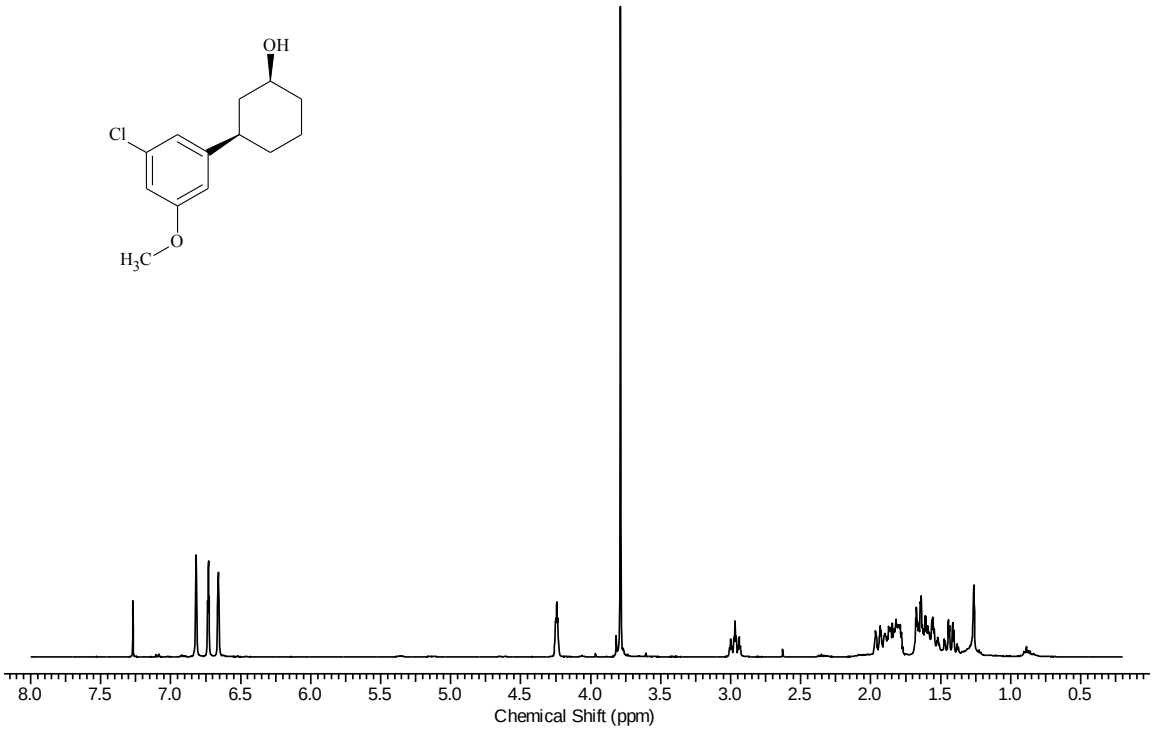
^{1}H NMR (400 MHz, $CDCl_3$) - **185**



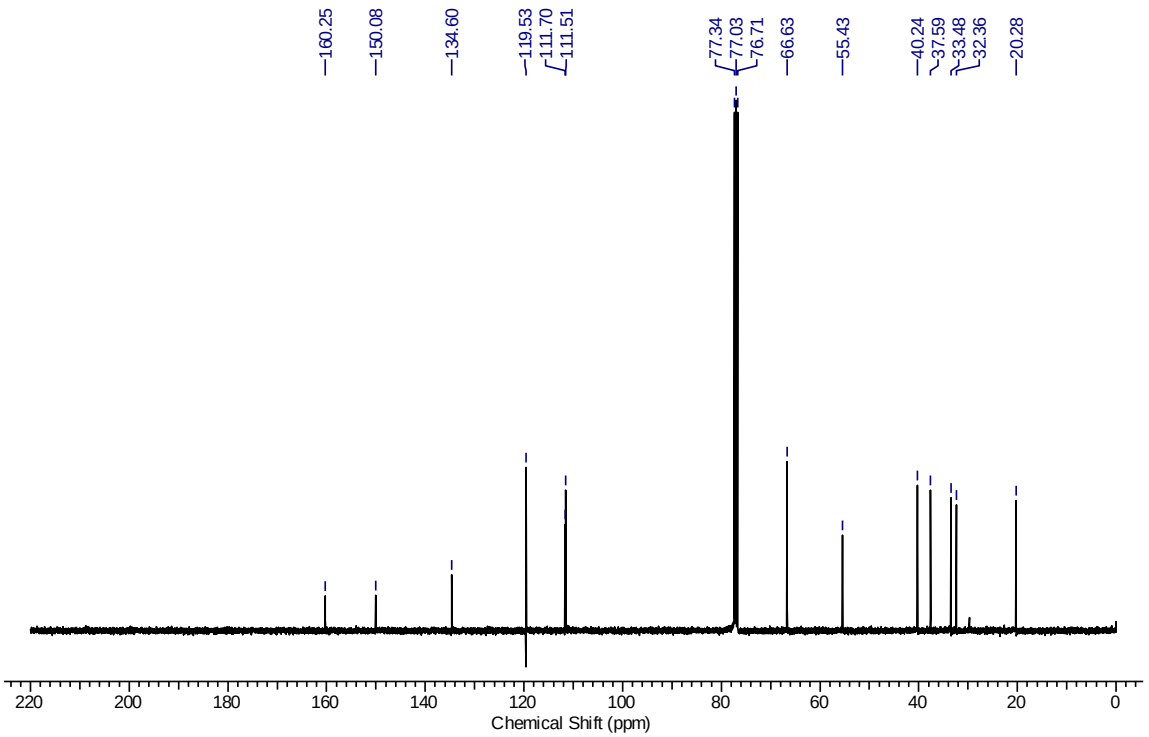
^{13}C NMR (101 MHz, $CDCl_3$) - **185**



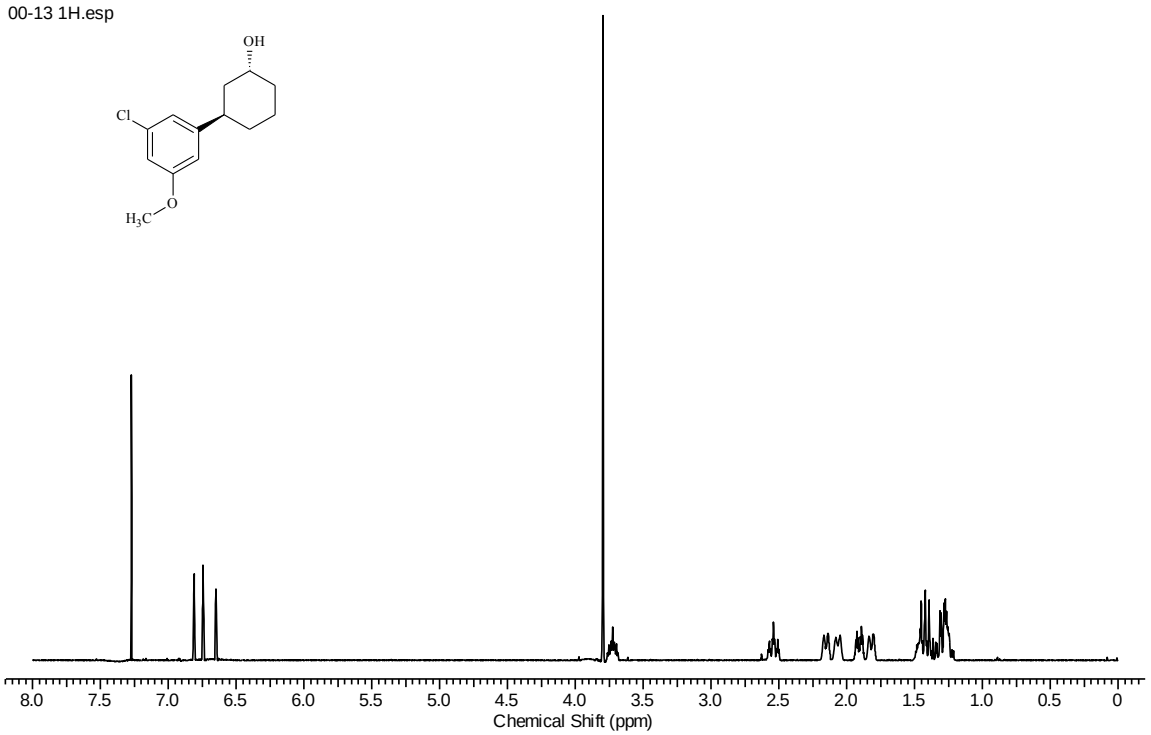
^{1}H NMR (400 MHz, $CDCl_3$) – *syn*-**204**



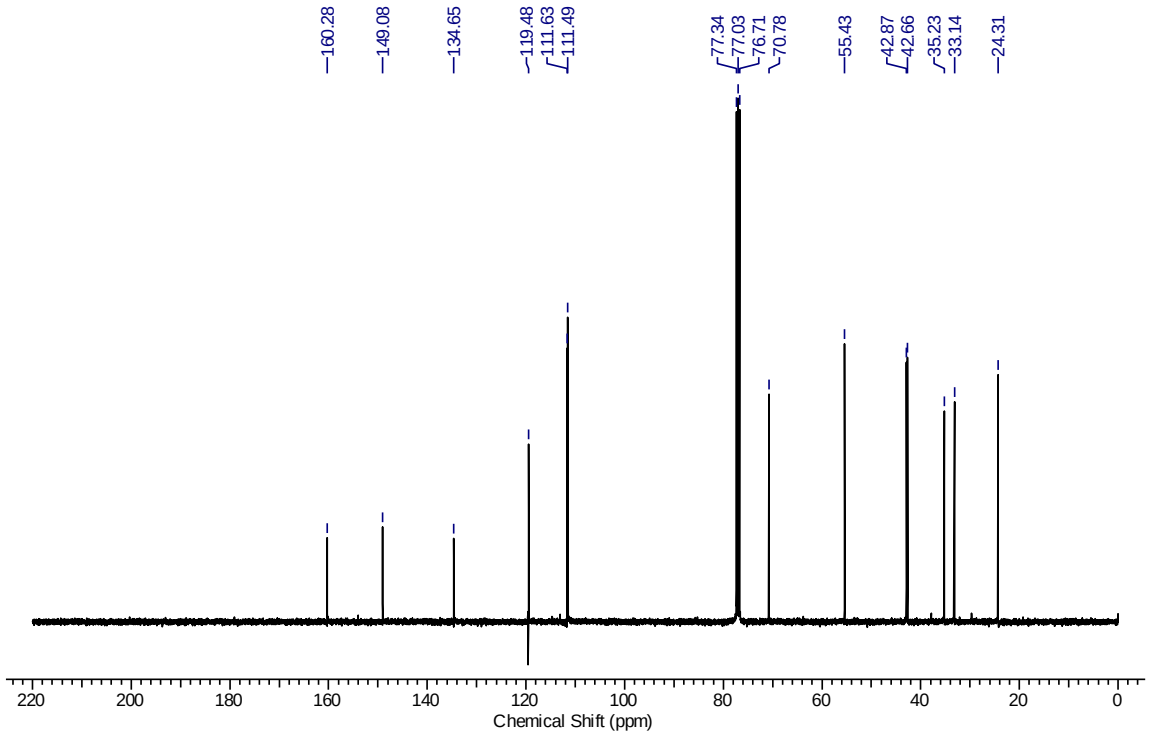
^{13}C NMR (101 MHz, $CDCl_3$) – *syn*-**204**



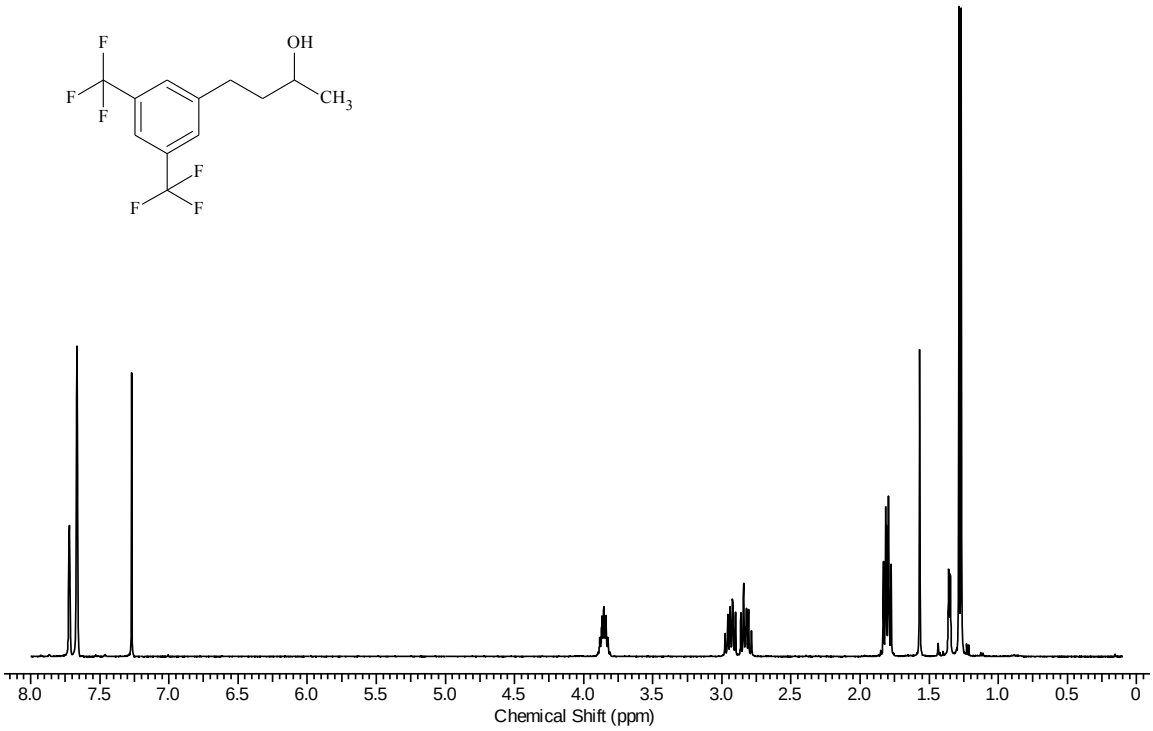
^{1}H NMR (400 MHz, $CDCl_3$) – *anti*-**204**



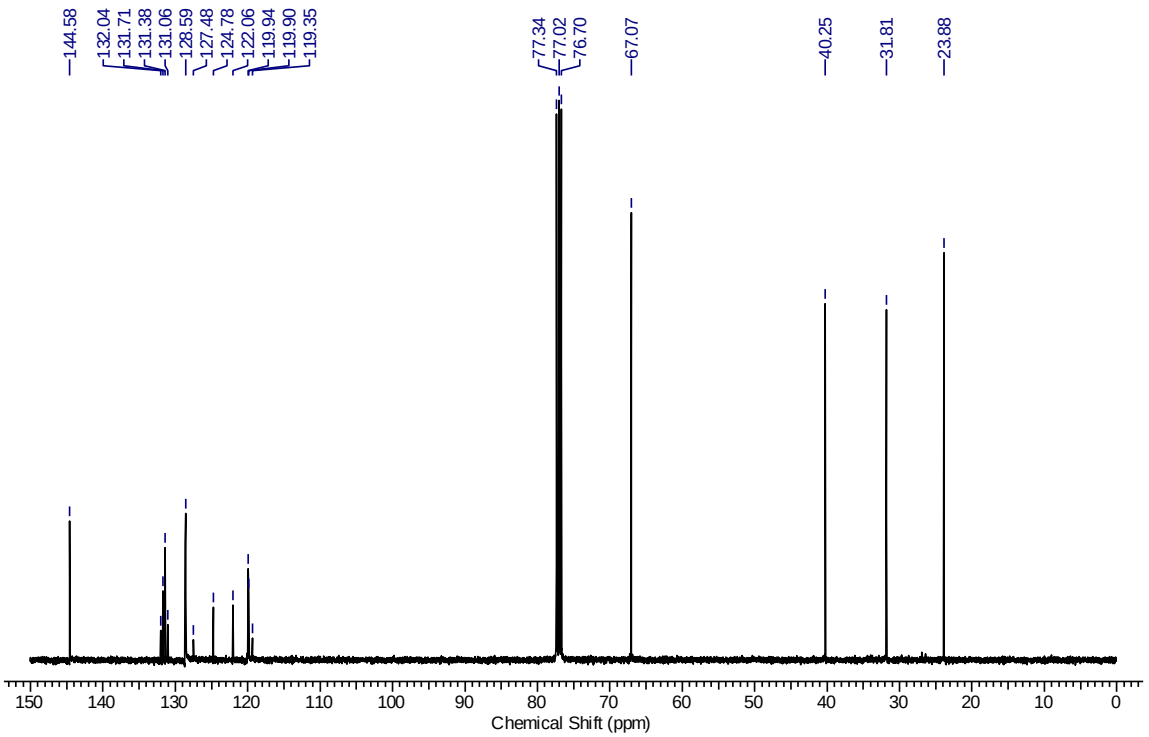
^{13}C NMR (101 MHz, $CDCl_3$) - *anti*-**204**



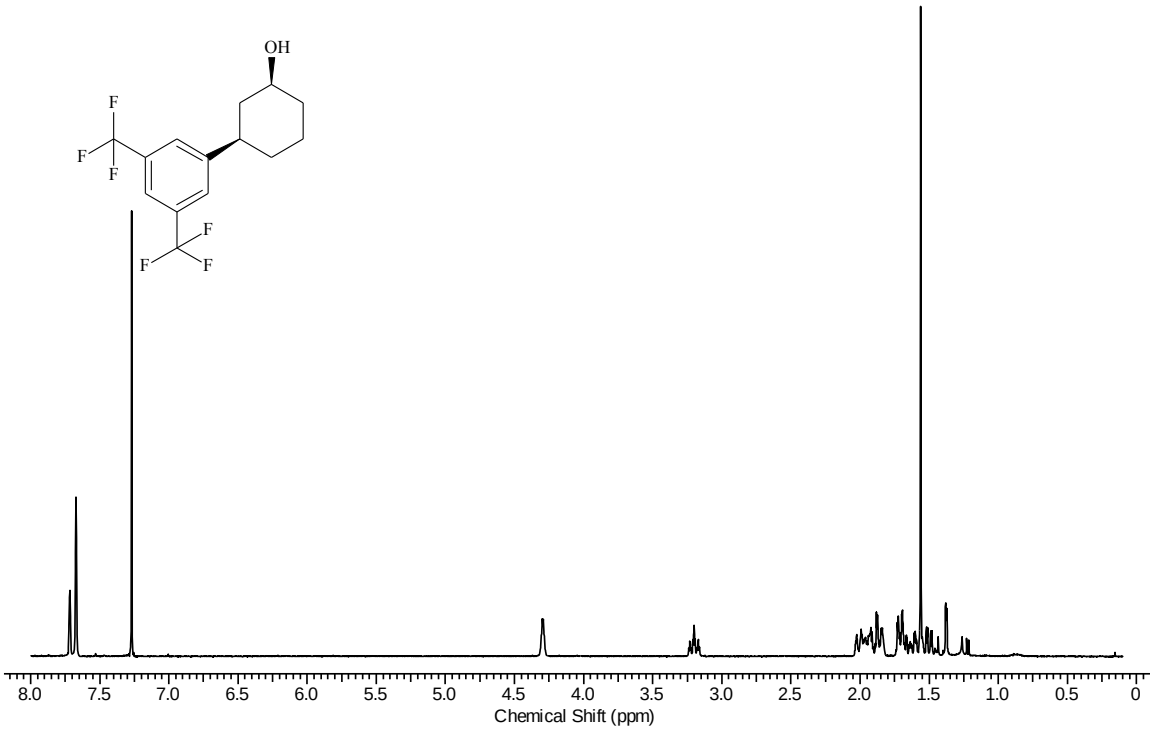
^{1}H NMR (400 MHz, $CDCl_3$) - **205**



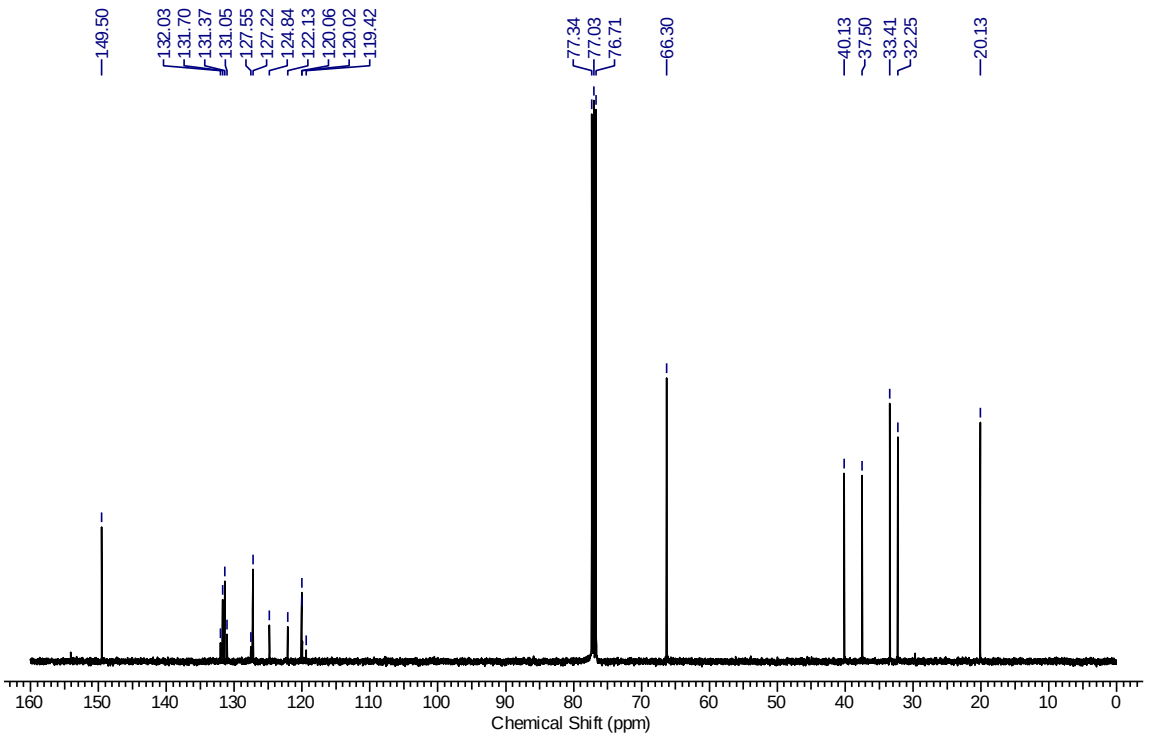
^{13}C NMR (101 MHz, $CDCl_3$) - **205**



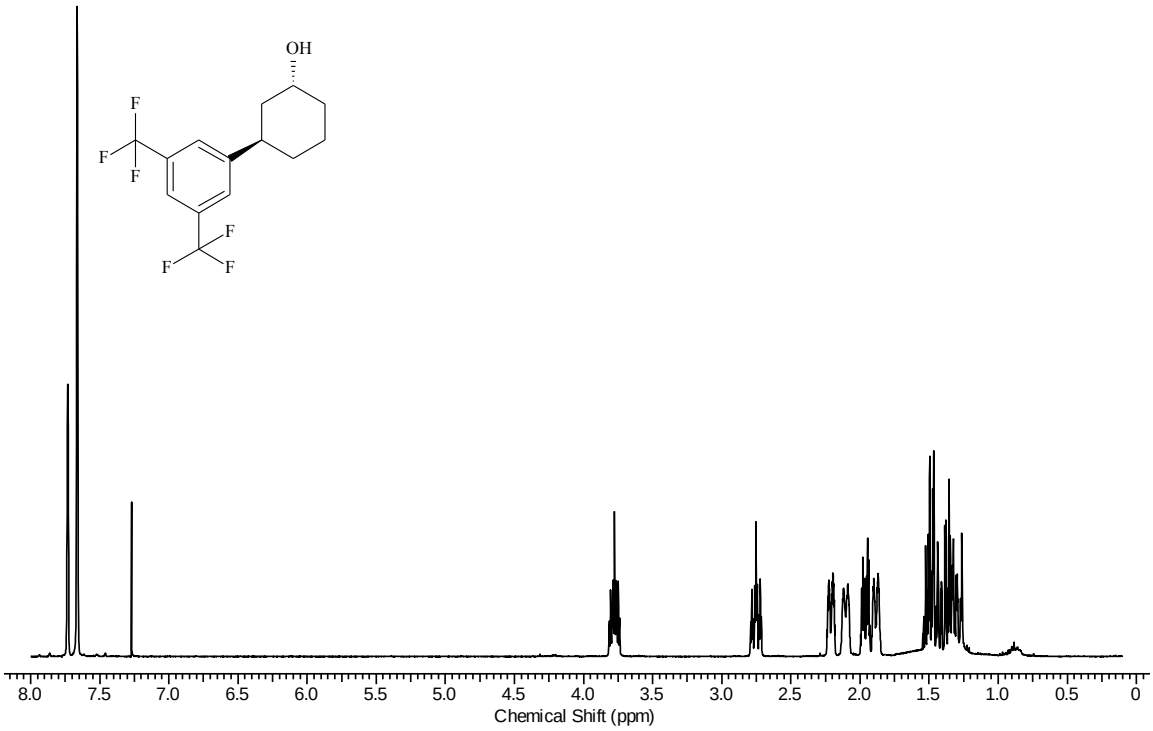
^{1}H NMR (400 MHz, $CDCl_3$) – *syn*-**206**



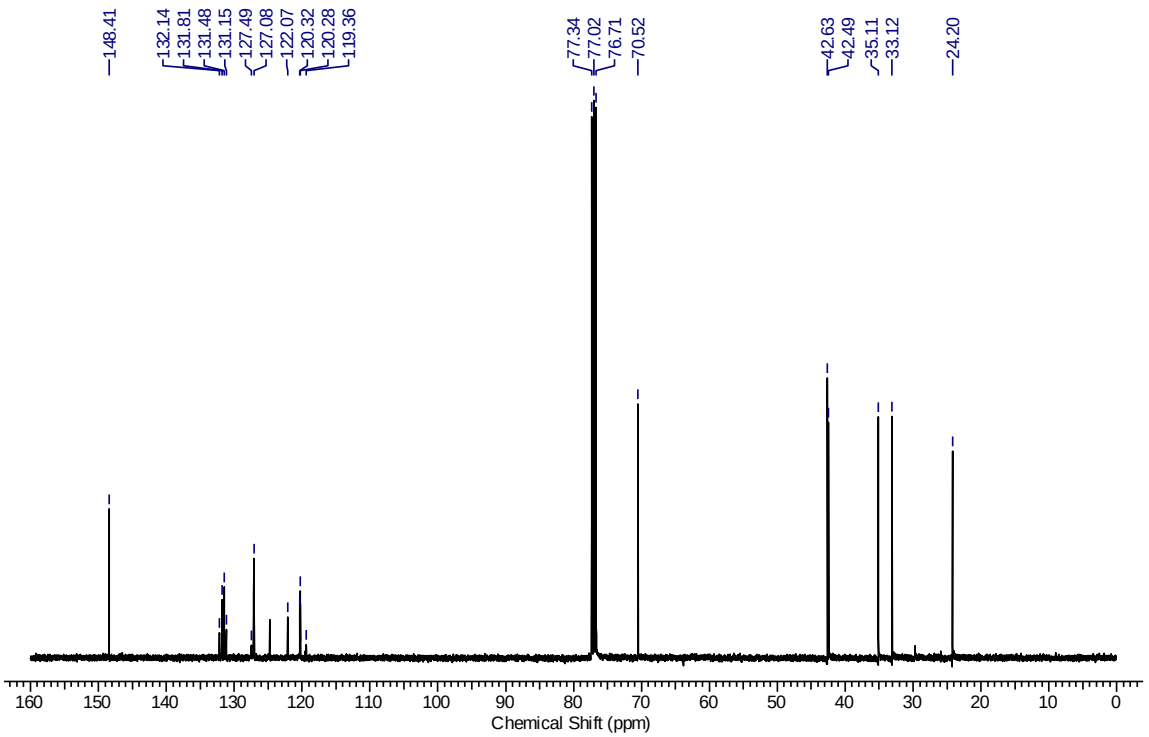
^{13}C NMR (101 MHz, $CDCl_3$) - *syn*-**206**



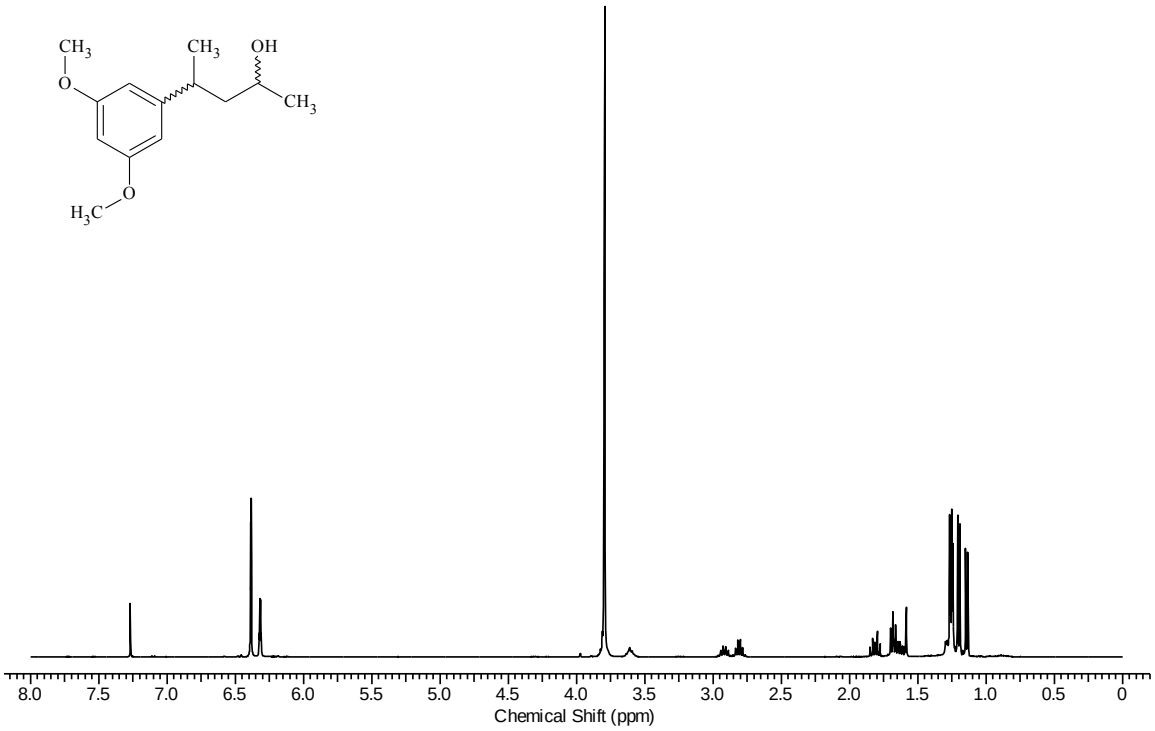
^{1}H NMR (400 MHz, $CDCl_3$) - *anti*-**206**



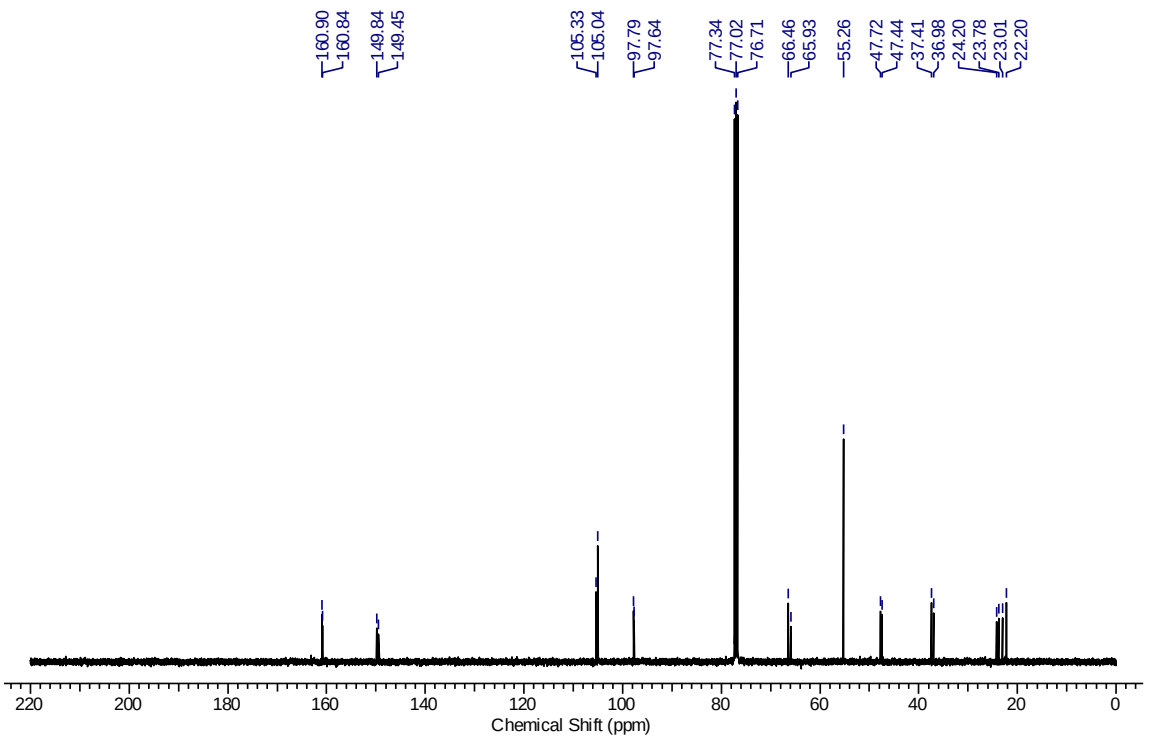
^{13}C NMR (101 MHz, $CDCl_3$) - *anti*-**206**



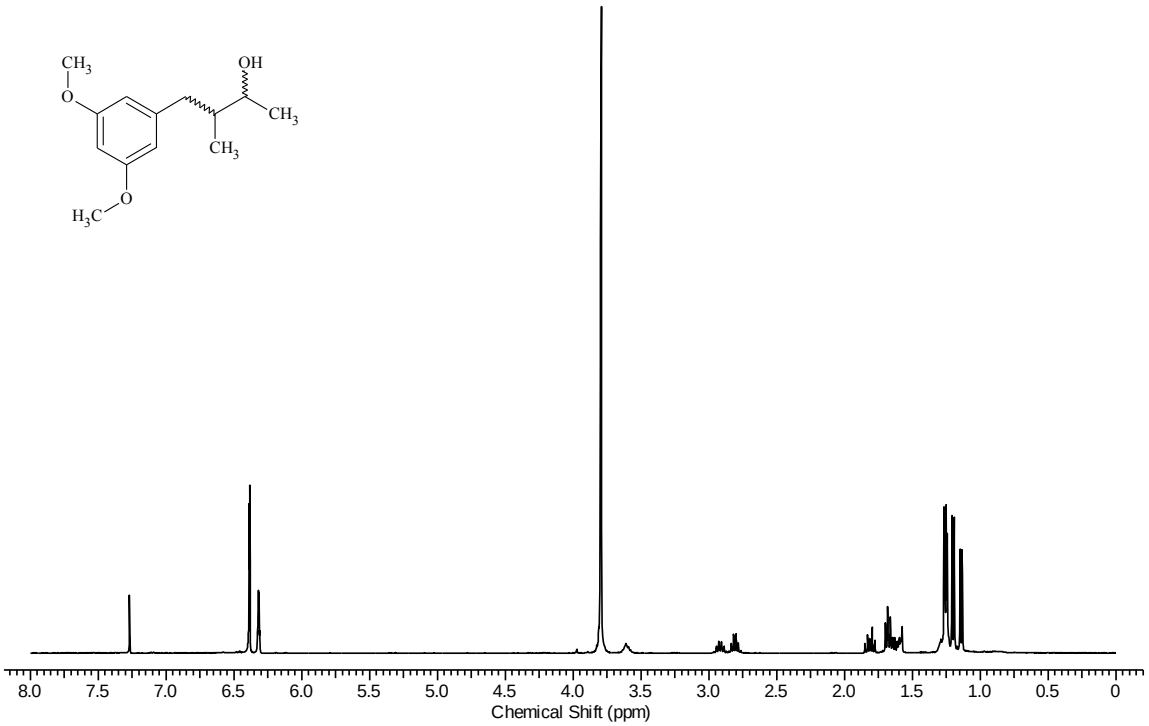
^{1}H NMR (400 MHz, $CDCl_3$) - **207**



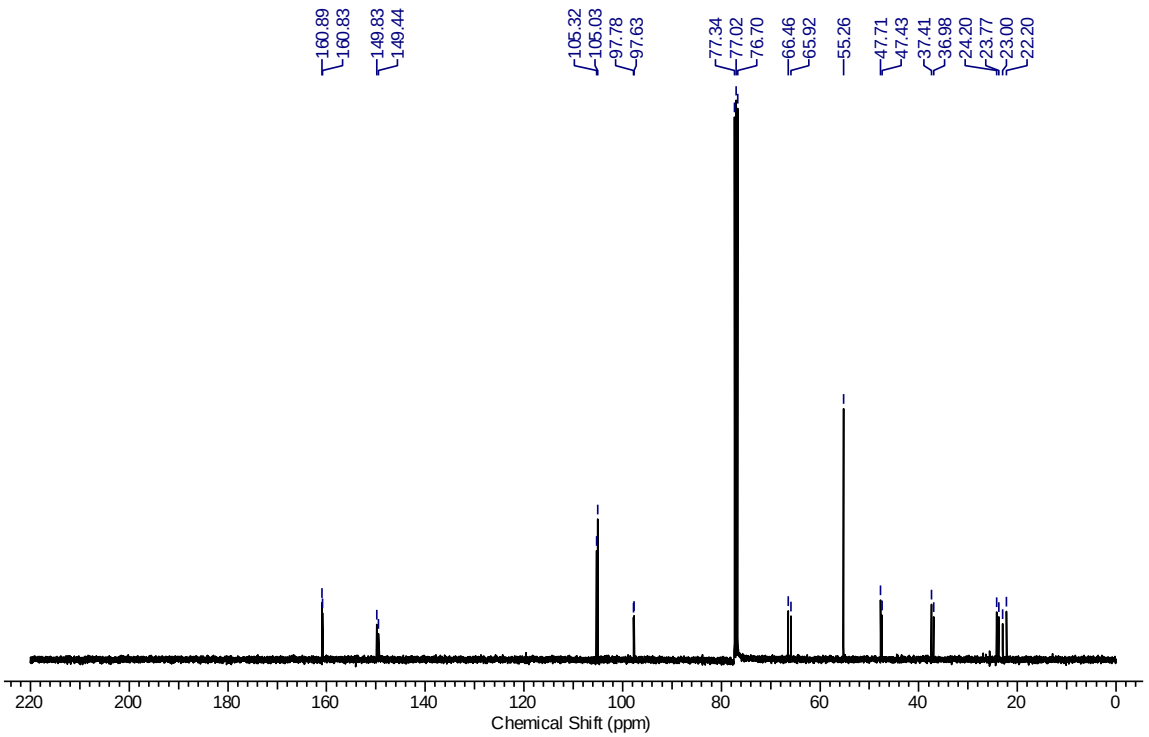
^{13}C NMR (101 MHz, $CDCl_3$) - **207**



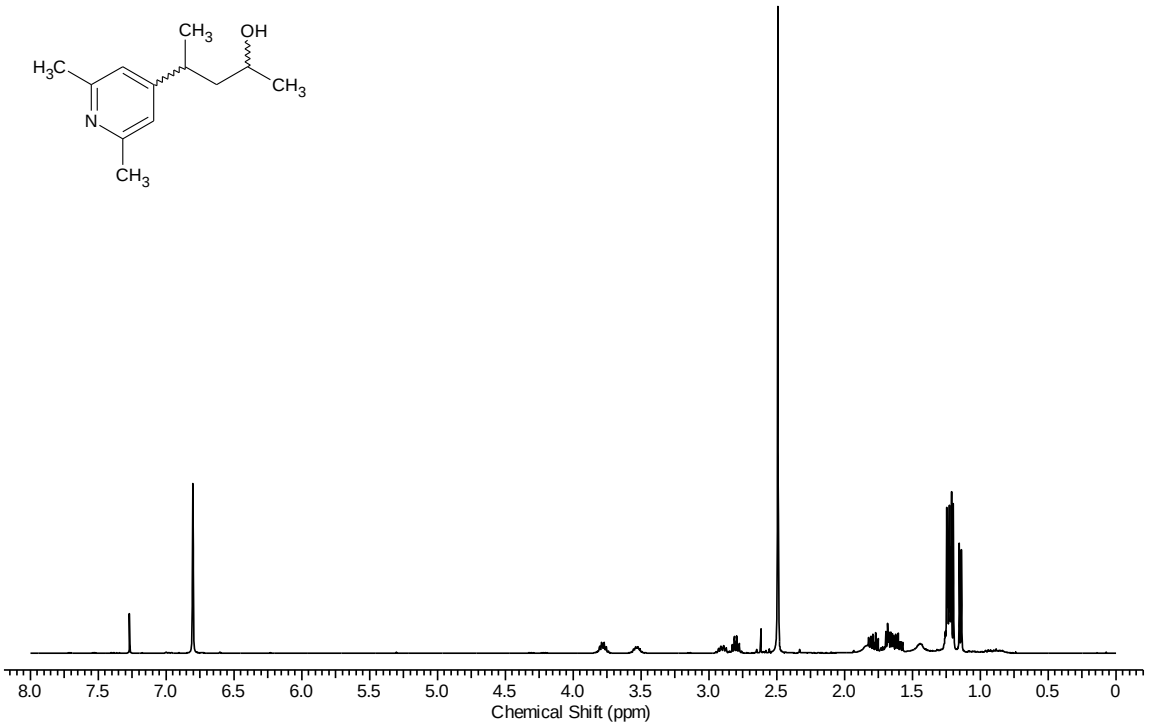
^{1}H NMR (400 MHz, $CDCl_3$) - **208**



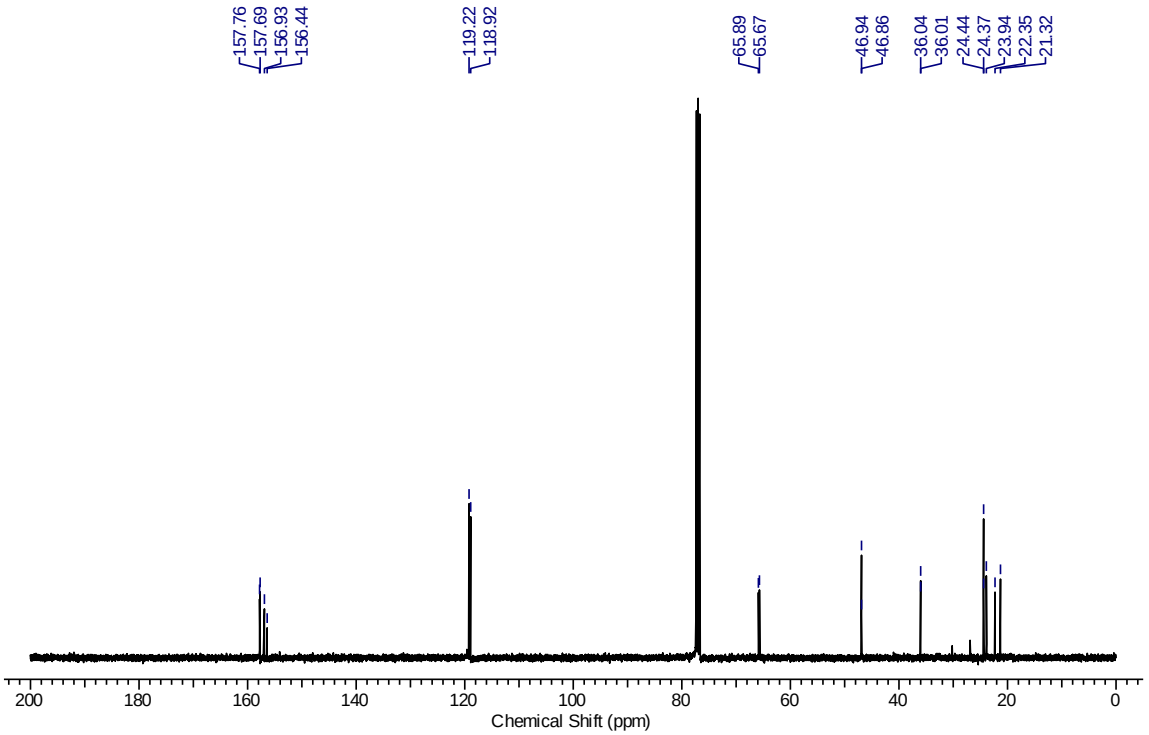
^{13}C NMR (101 MHz, $CDCl_3$) - **208**



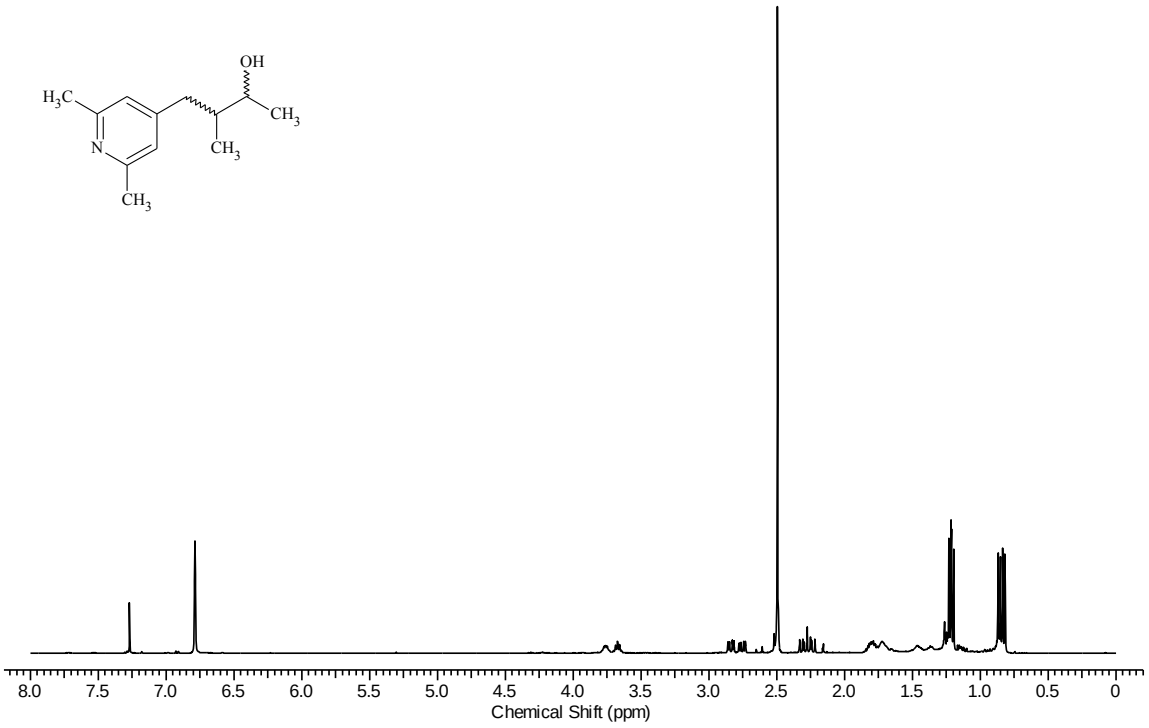
^{1}H NMR (400 MHz, $CDCl_3$) - **209**



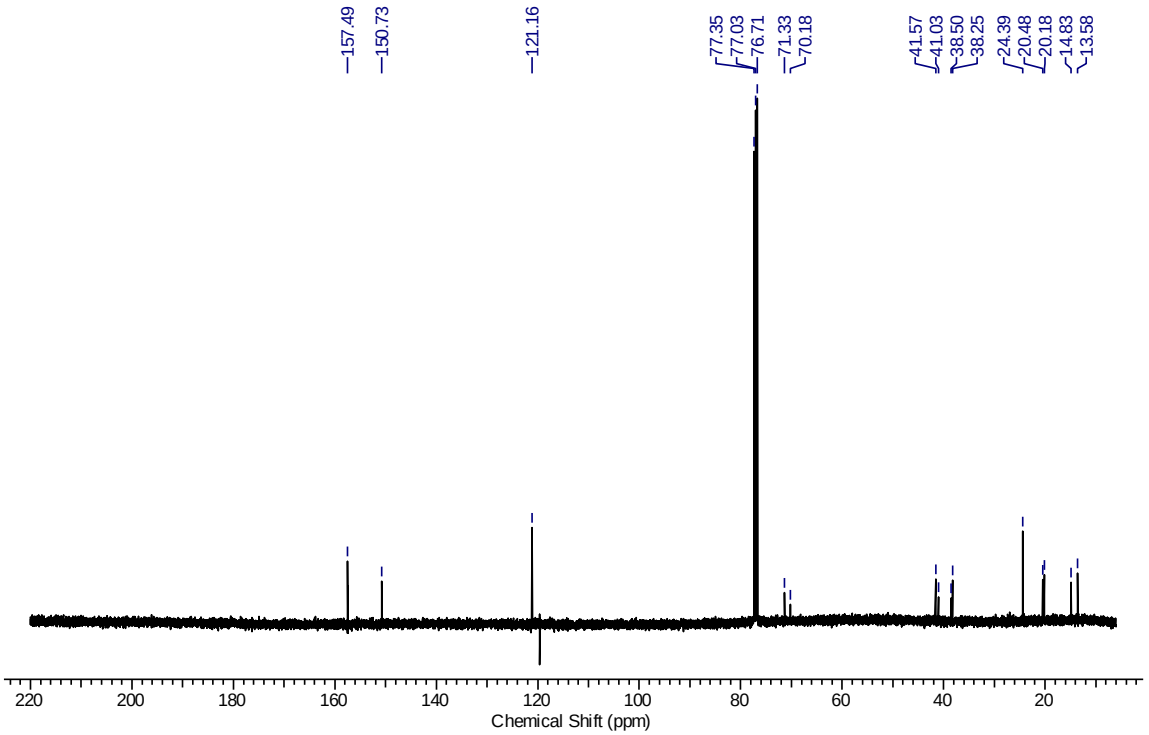
^{13}C NMR (101 MHz, $CDCl_3$) - **209**



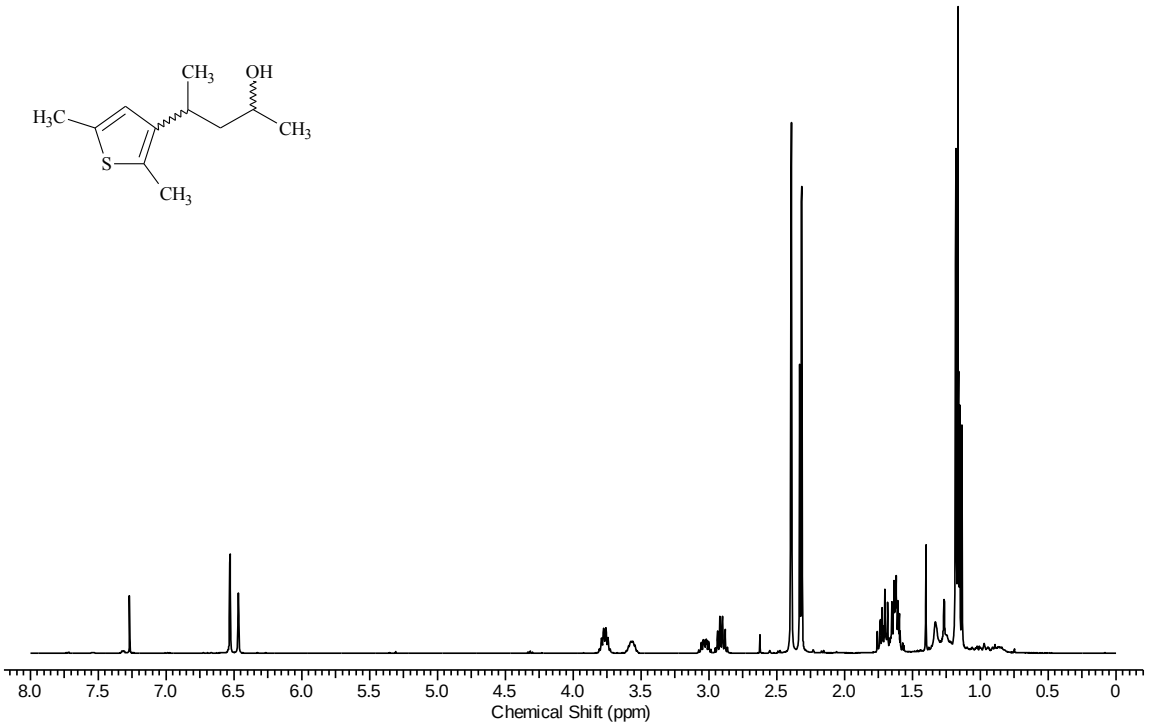
^{1}H NMR (400 MHz, $CDCl_3$) - **210**



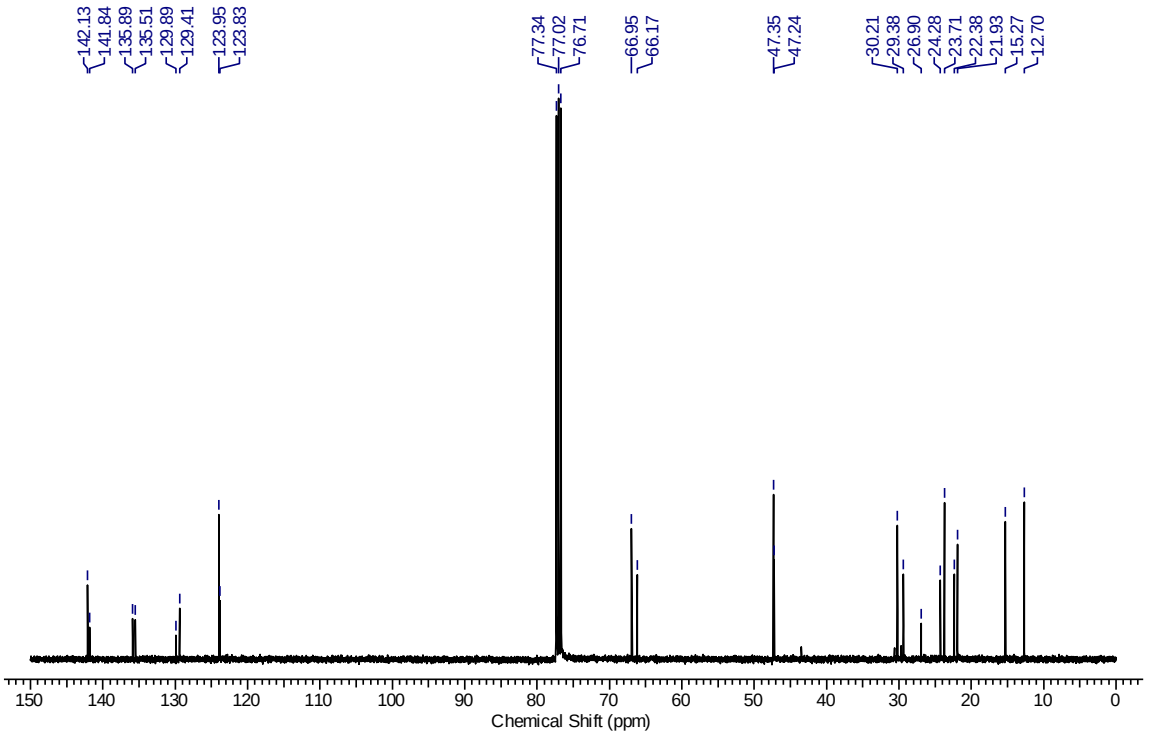
^{13}C NMR (101 MHz, $CDCl_3$) - **210**



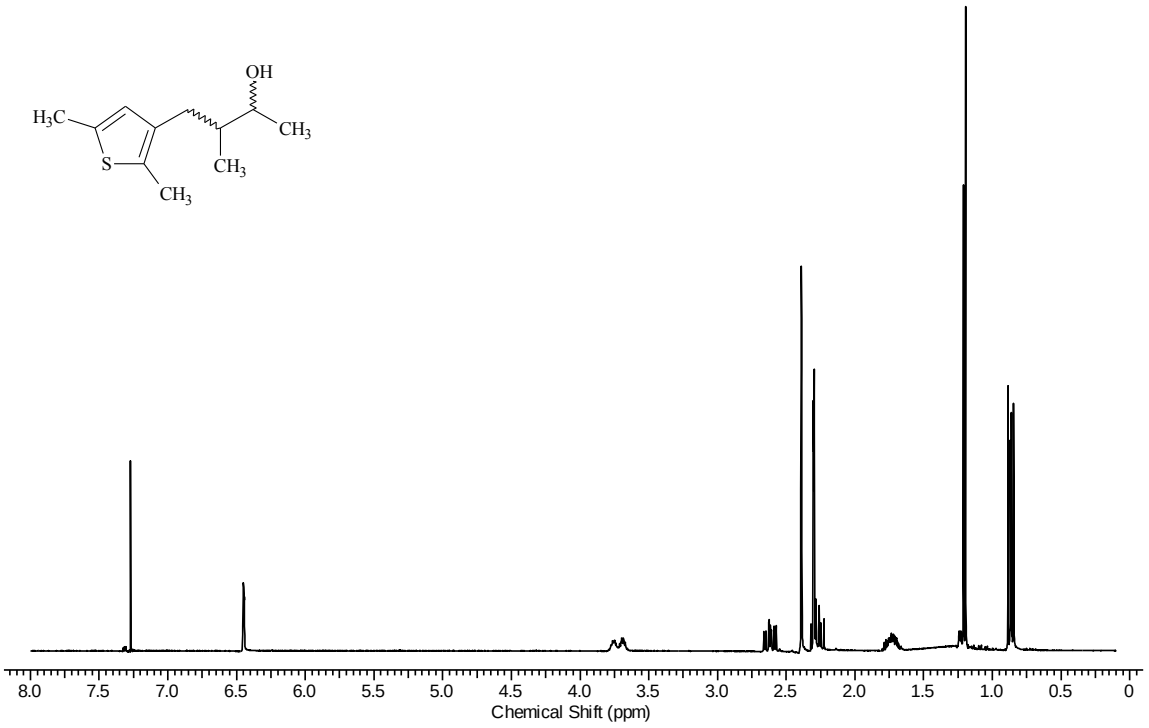
^{1}H NMR (400 MHz, $CDCl_3$) - **211**



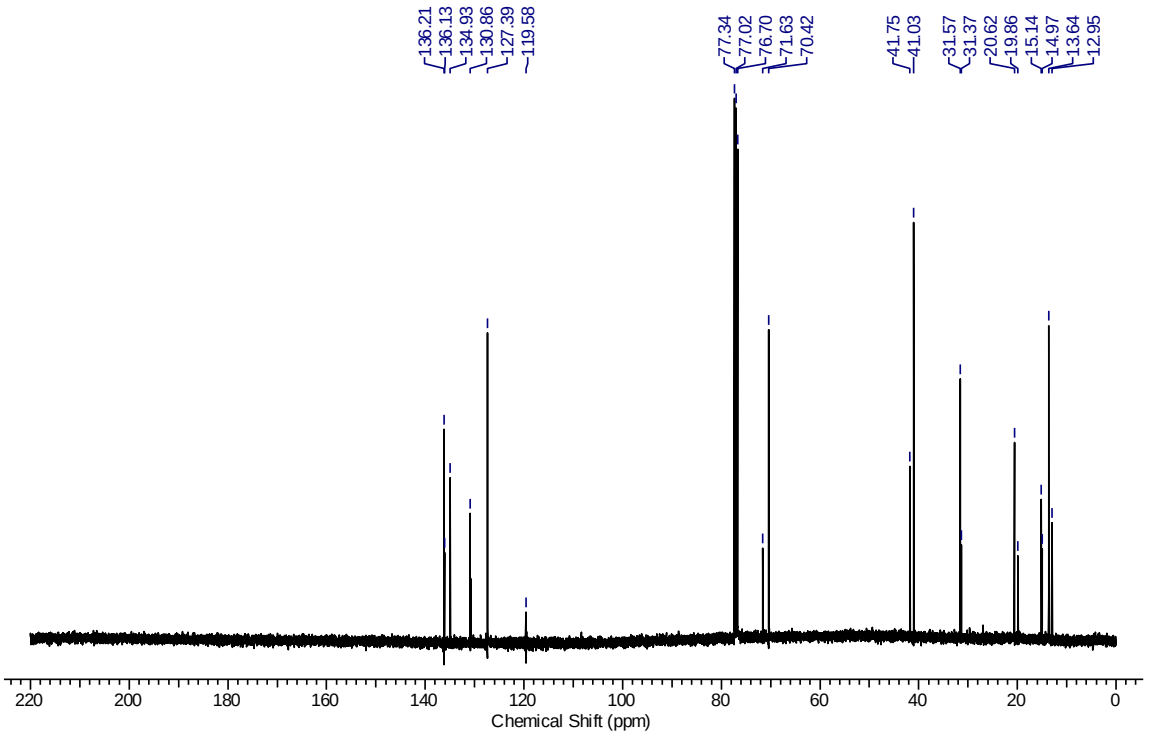
^{13}C NMR (101 MHz, $CDCl_3$) - **211**



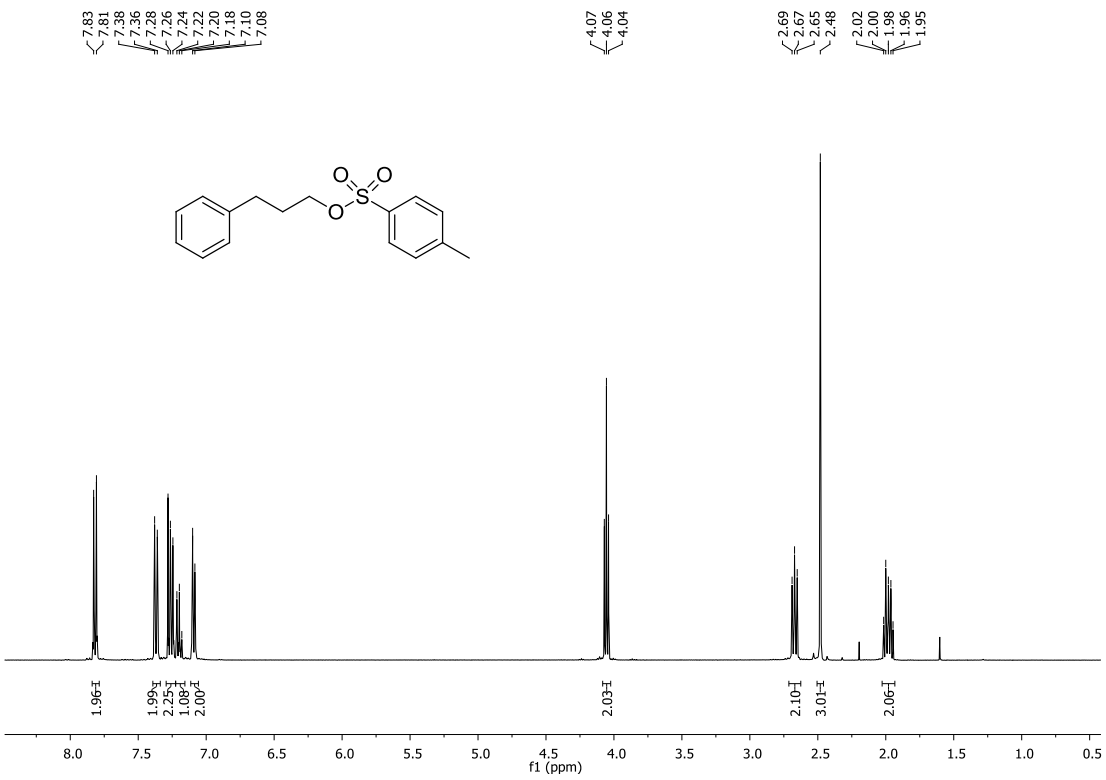
^{1}H NMR (400 MHz, $CDCl_3$) - **212**



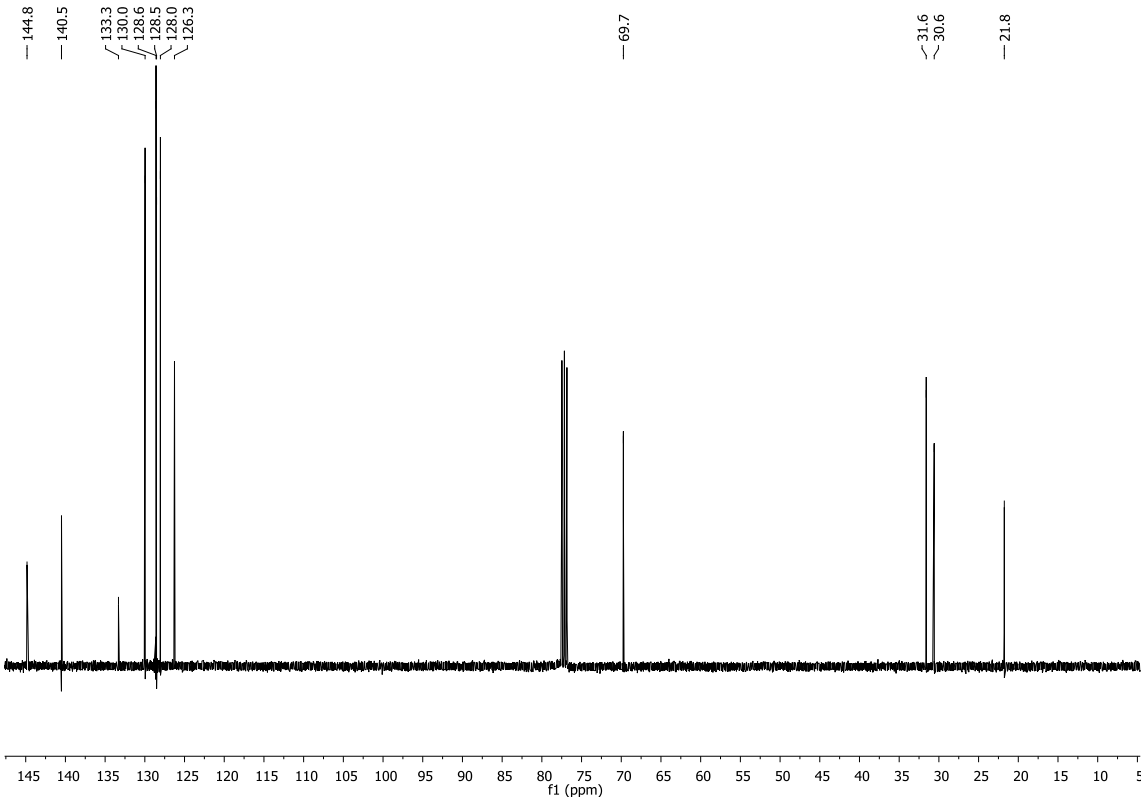
^{13}C NMR (101 MHz, $CDCl_3$) - **212**



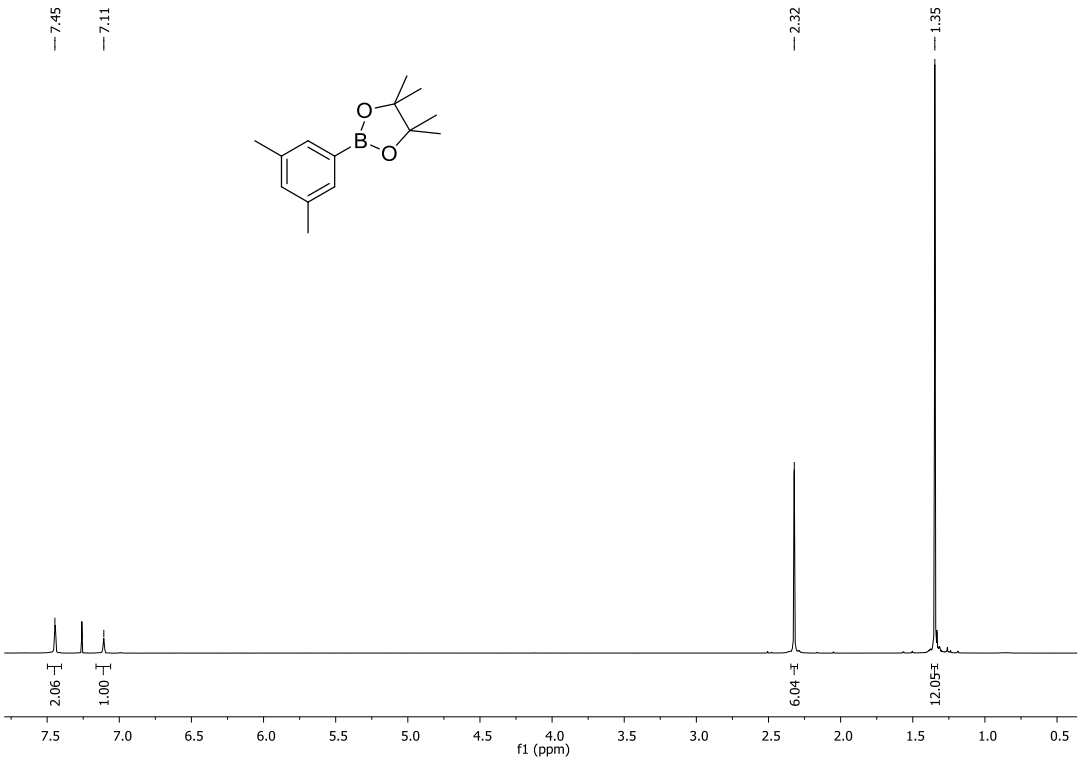
^{1}H NMR (400 MHz, $CDCl_3$) - **240**



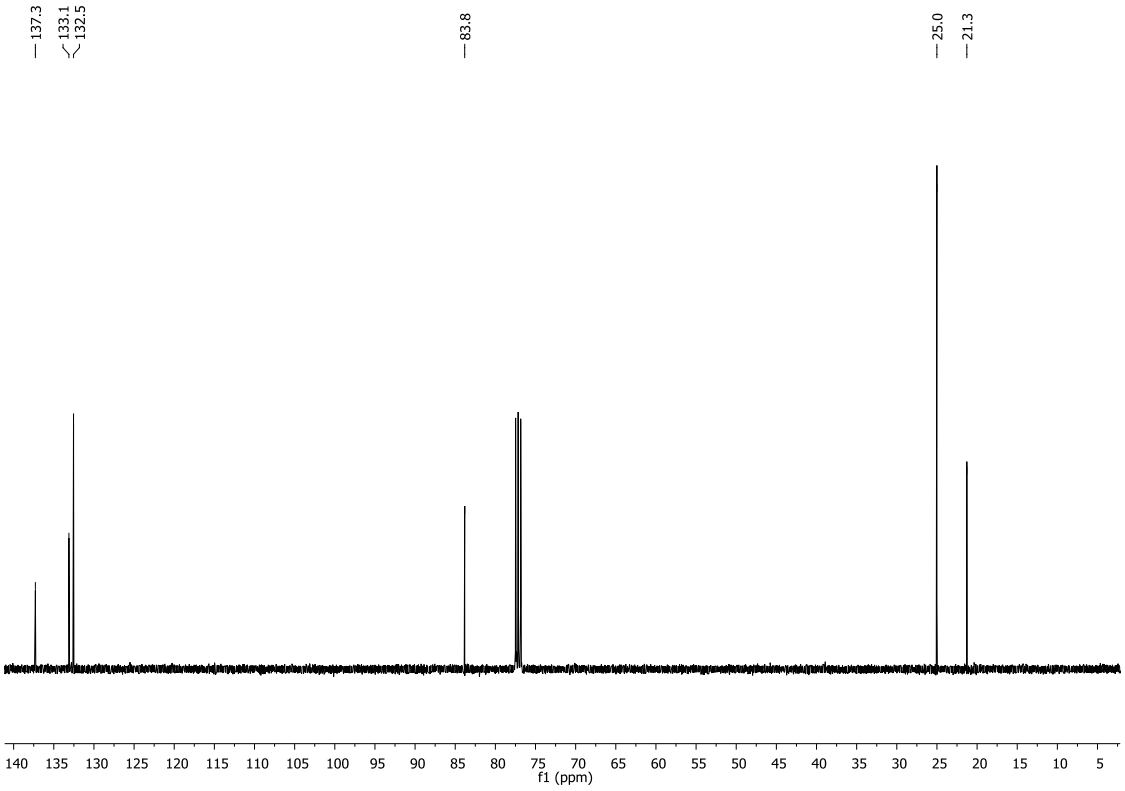
^{13}C NMR (101 MHz, $CDCl_3$) - **240**



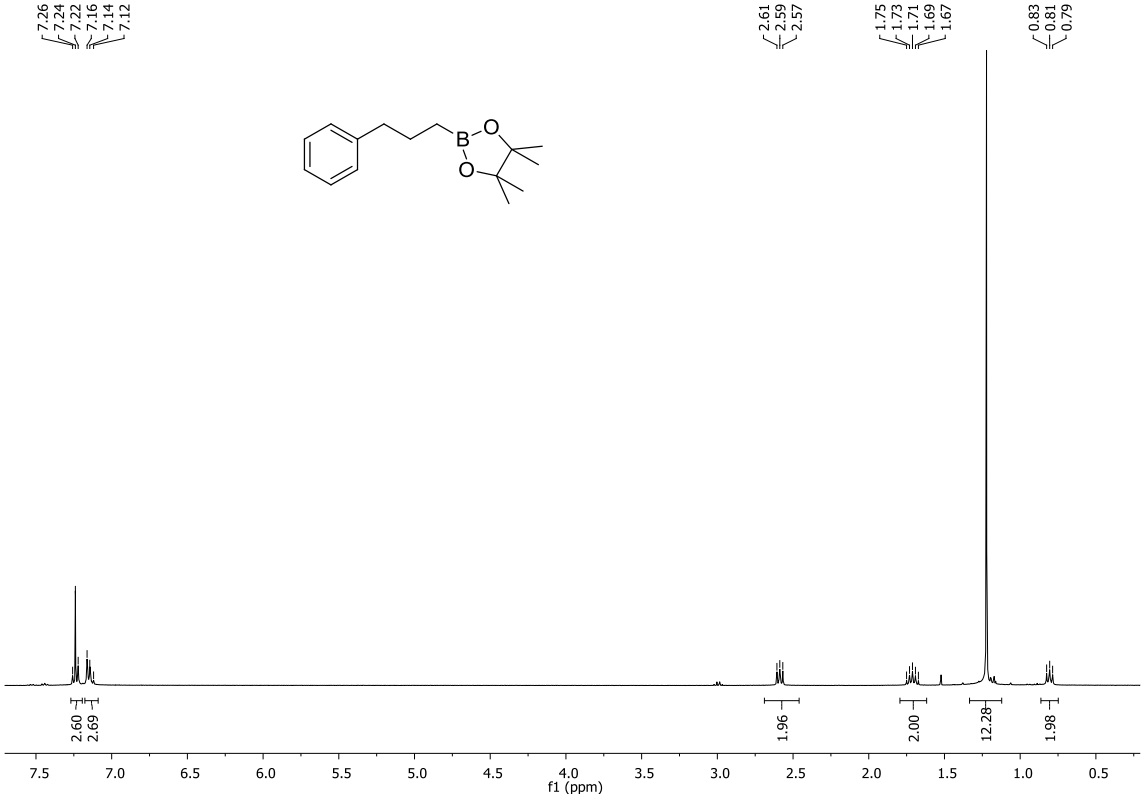
^{1}H NMR (400 MHz, $CDCl_3$) - **19**



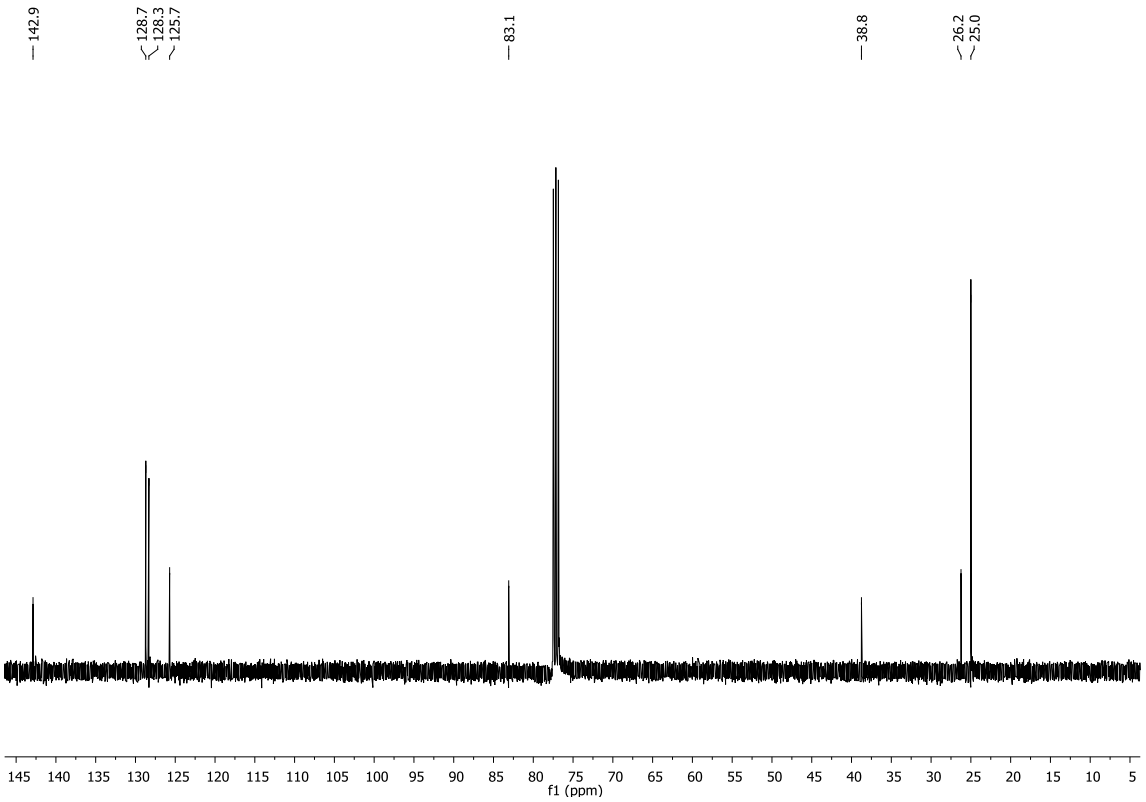
^{13}C NMR (101 MHz, $CDCl_3$) - **19**



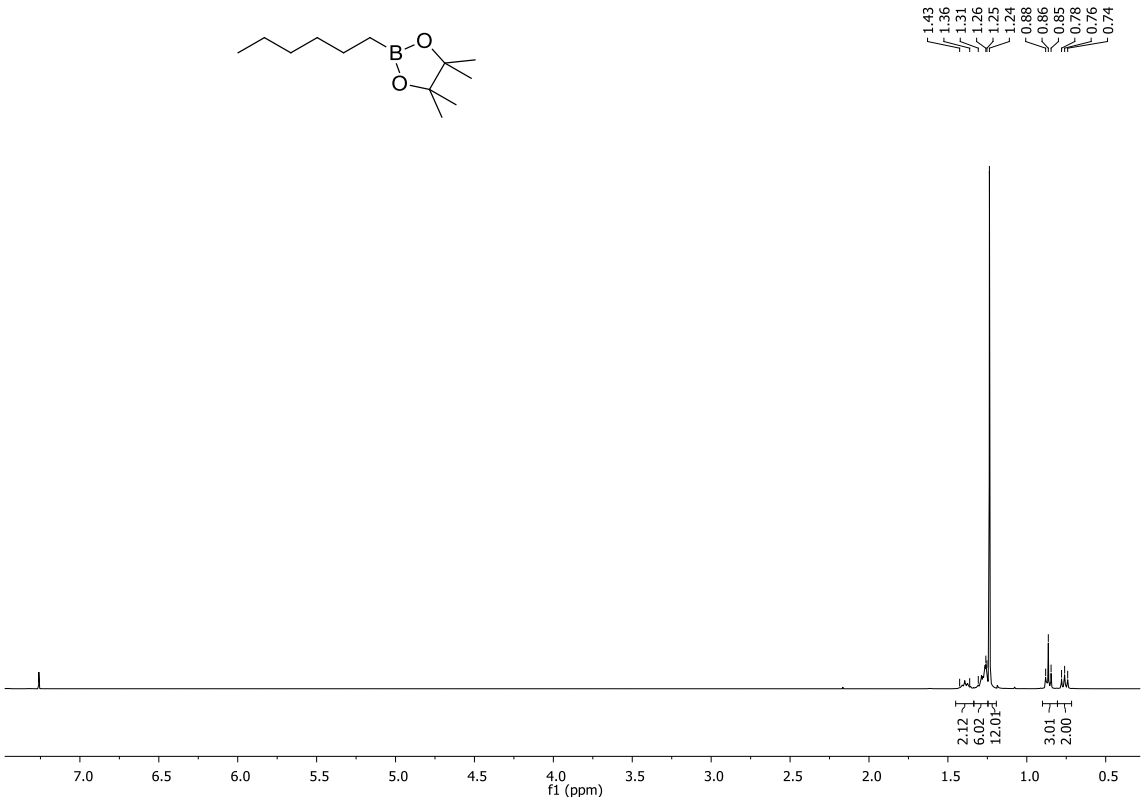
^{1}H NMR (400 MHz, $CDCl_3$) - **243**



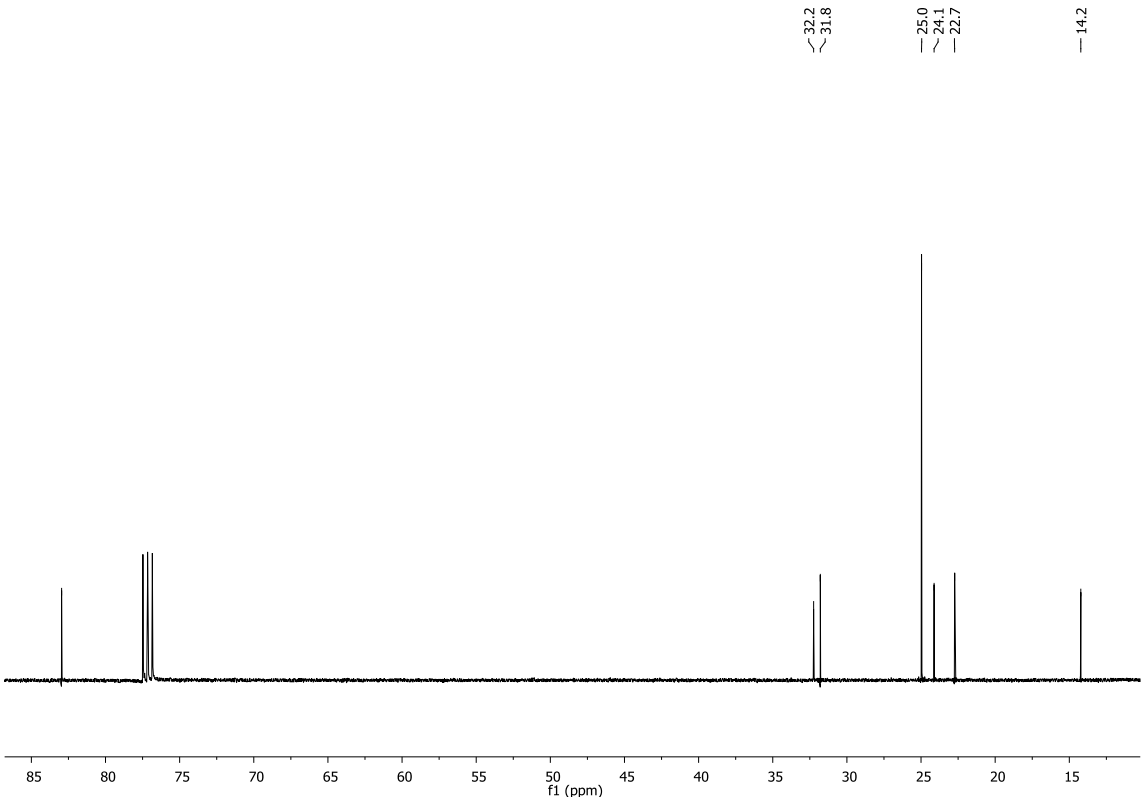
^{13}C NMR (101 MHz, $CDCl_3$) - **243**



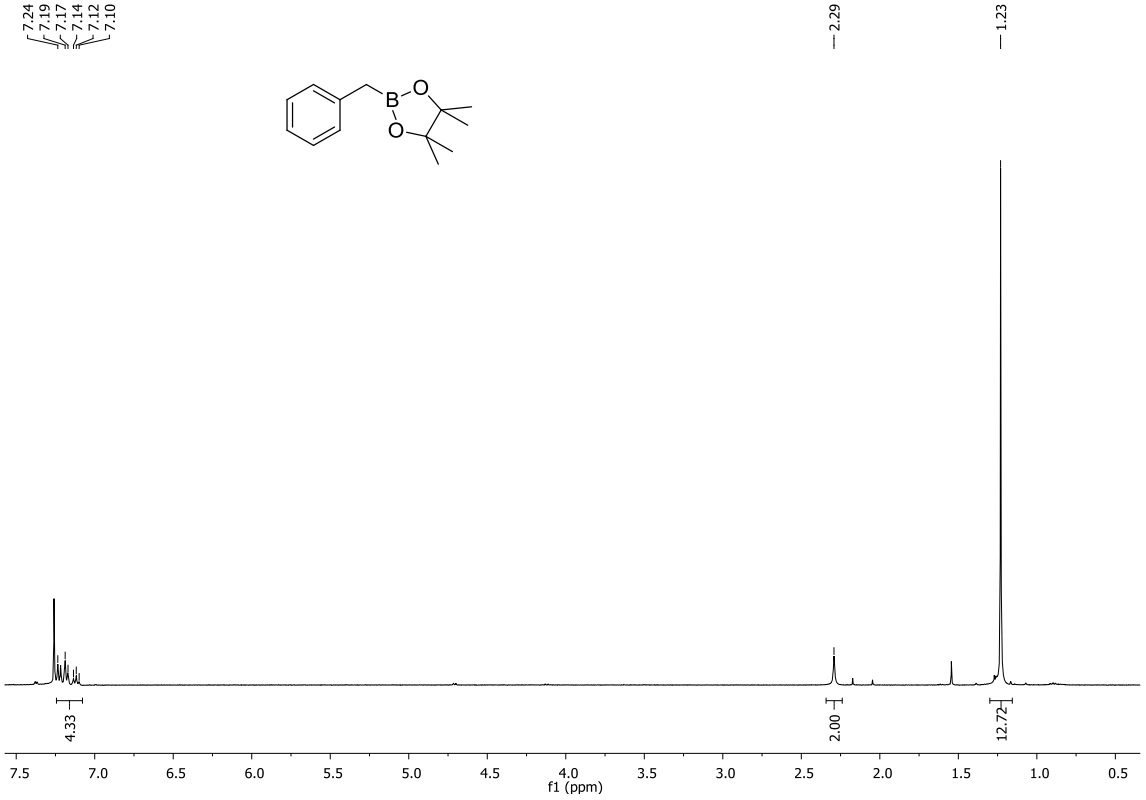
^{1}H NMR (400 MHz, $CDCl_3$) - **238**



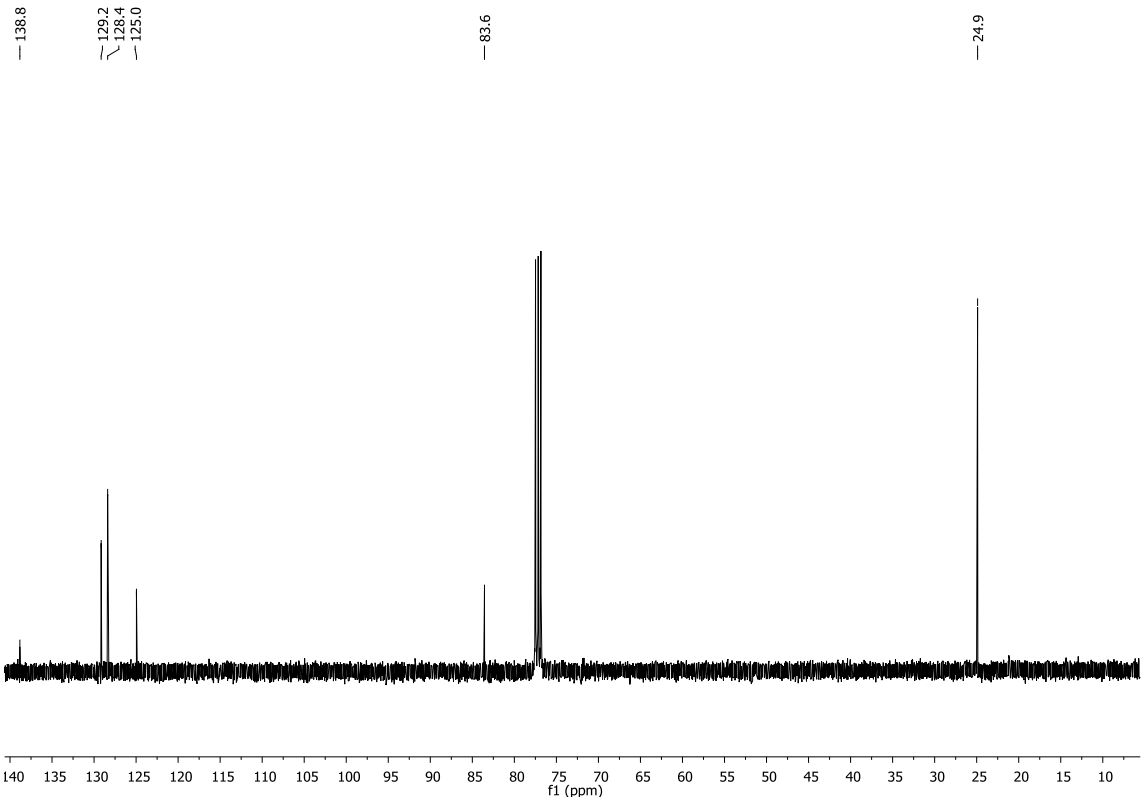
^{13}C NMR (101 MHz, $CDCl_3$) – **238**



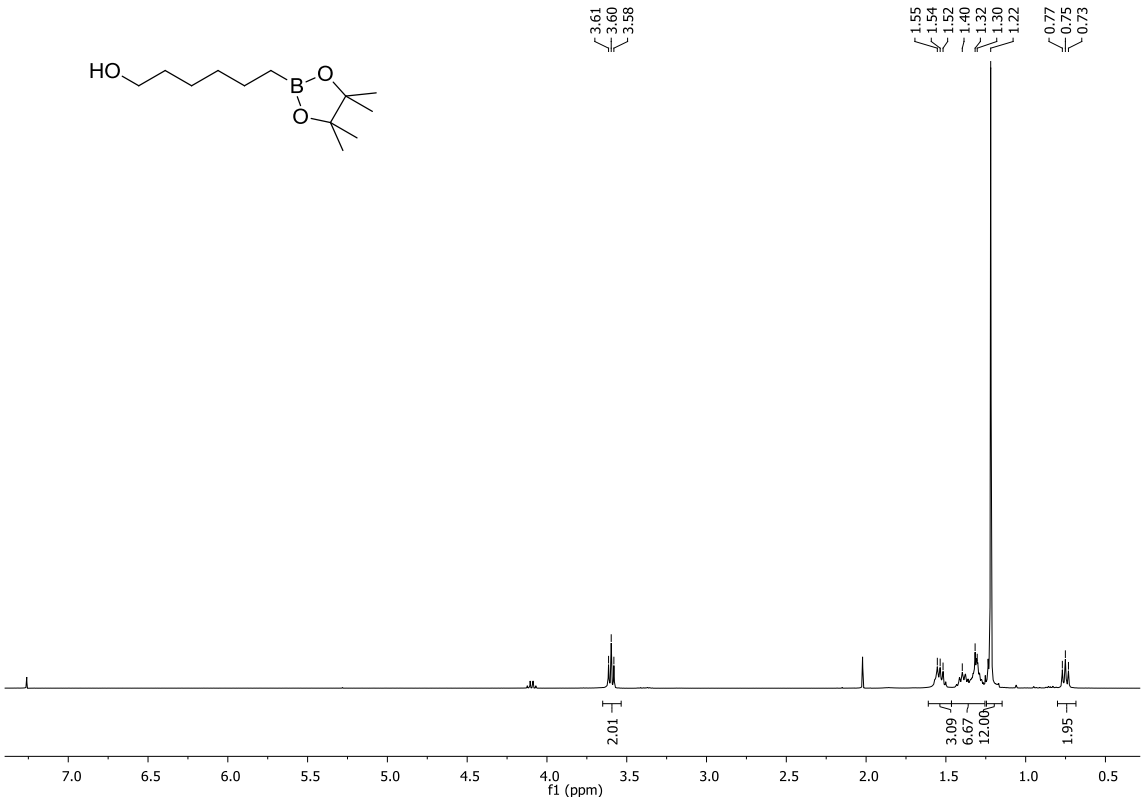
^{1}H NMR (400 MHz, $CDCl_3$) - **260**



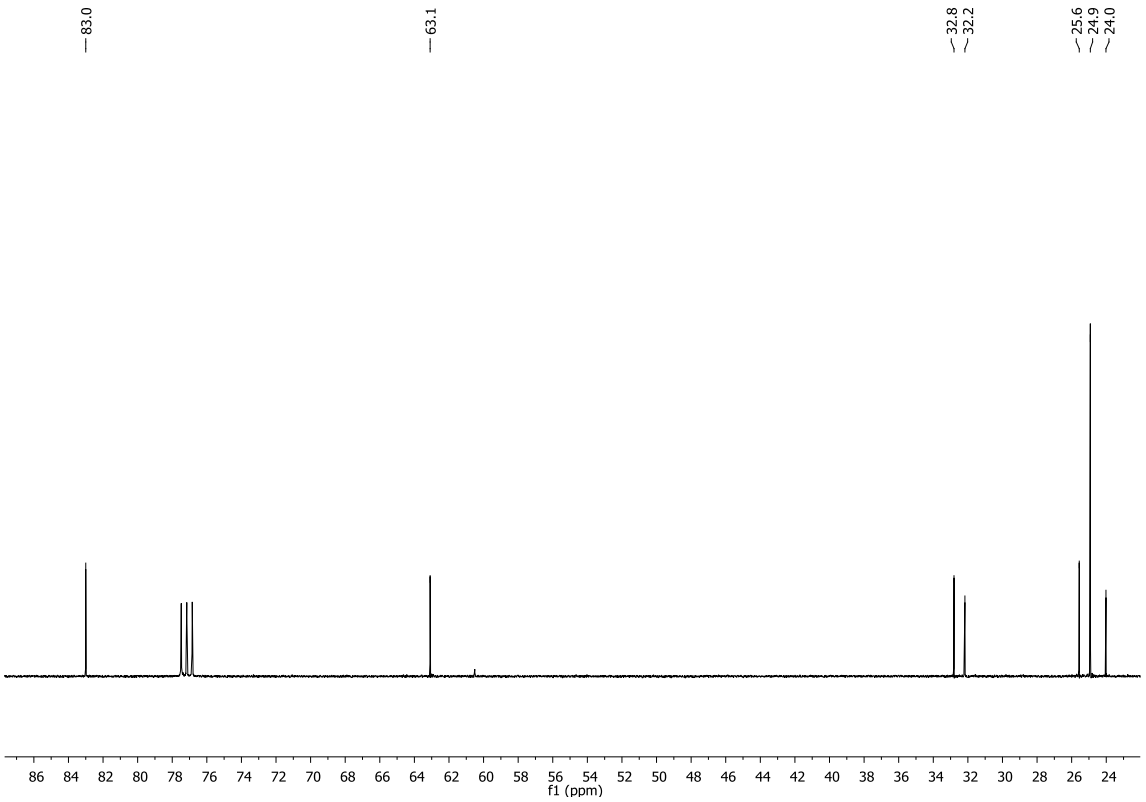
^{13}C NMR (101 MHz, $CDCl_3$) – **260**



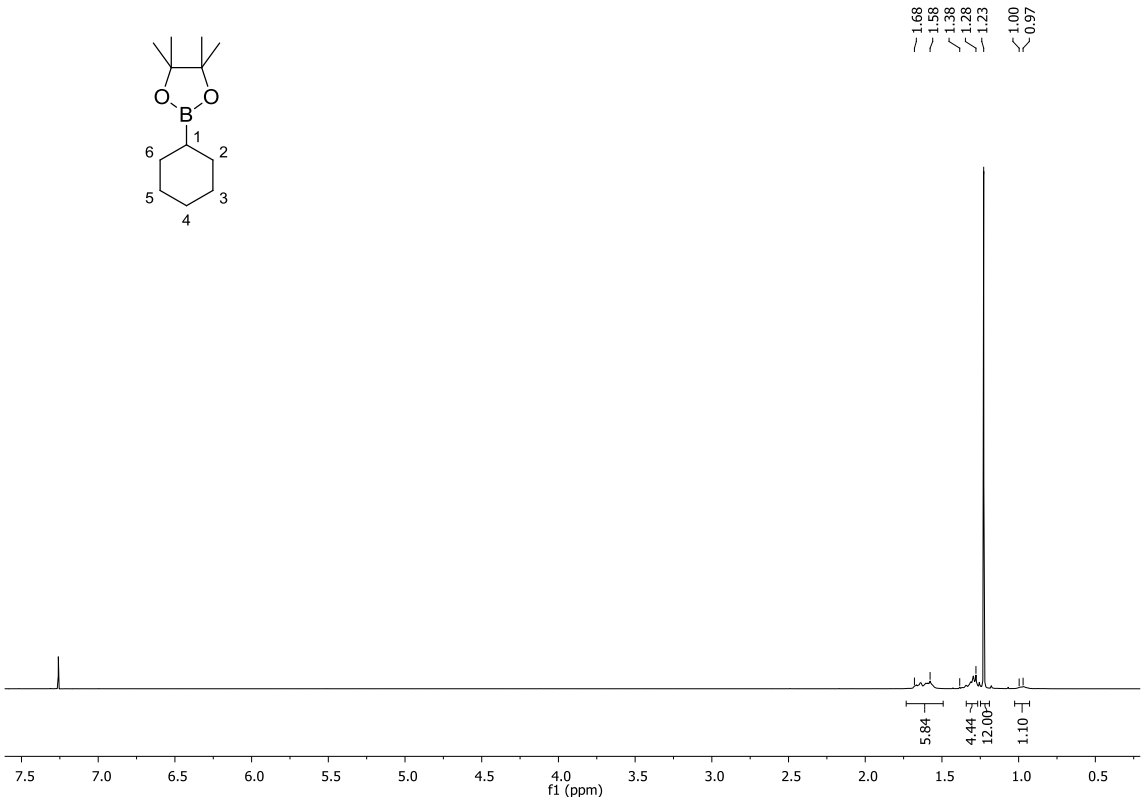
^{1}H NMR (400 MHz, $CDCl_3$) - **265**



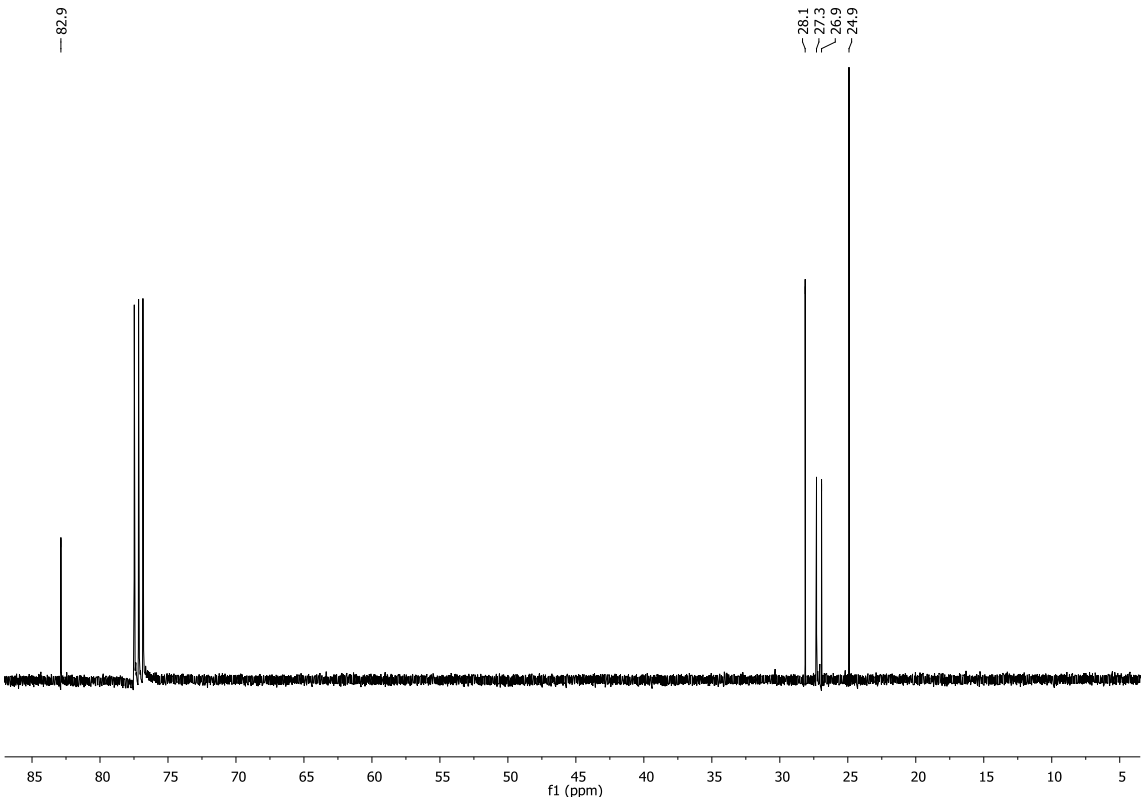
^{13}C NMR (101 MHz, $CDCl_3$) – **265**



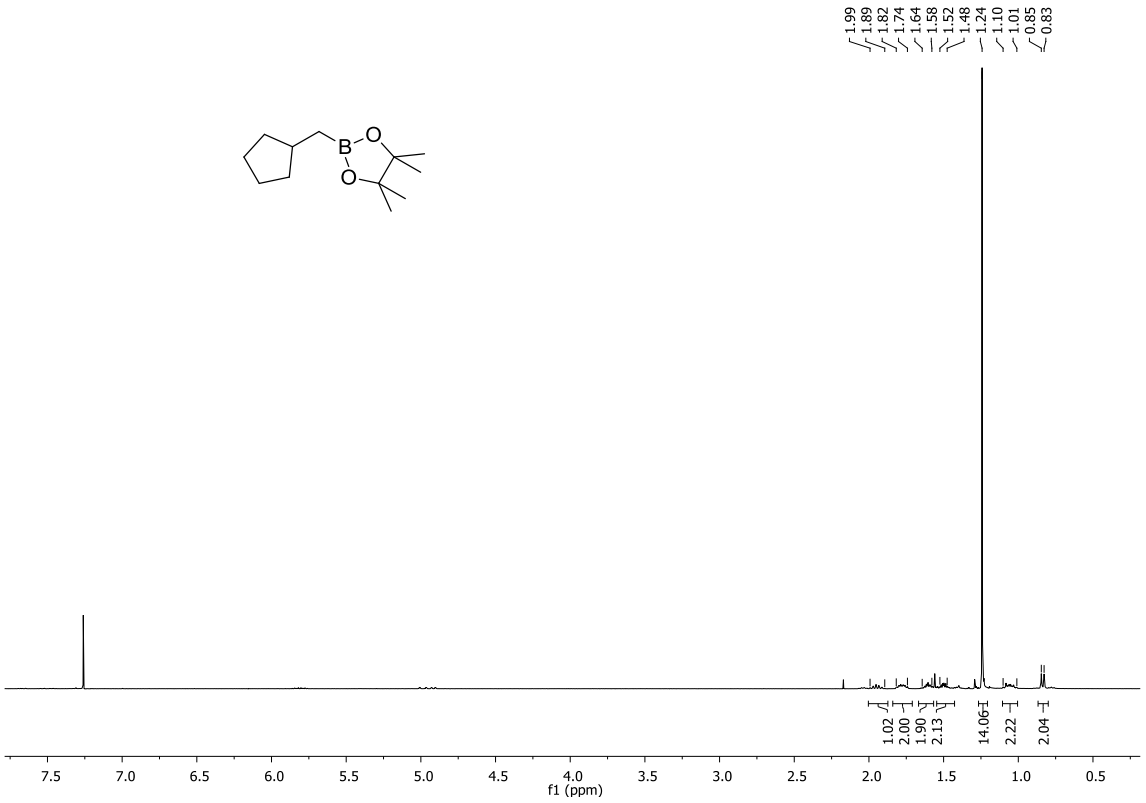
^{1}H NMR (400 MHz, $CDCl_3$) - **270**



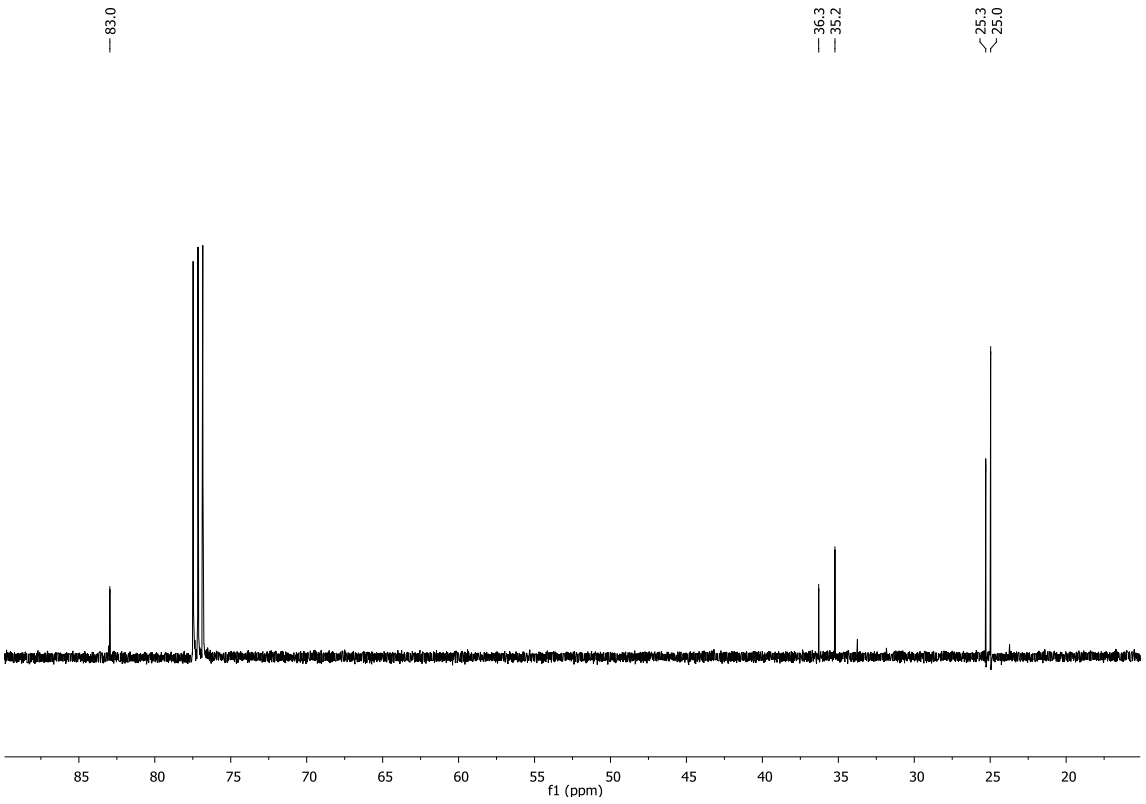
^{13}C NMR (101 MHz, $CDCl_3$) – **270**



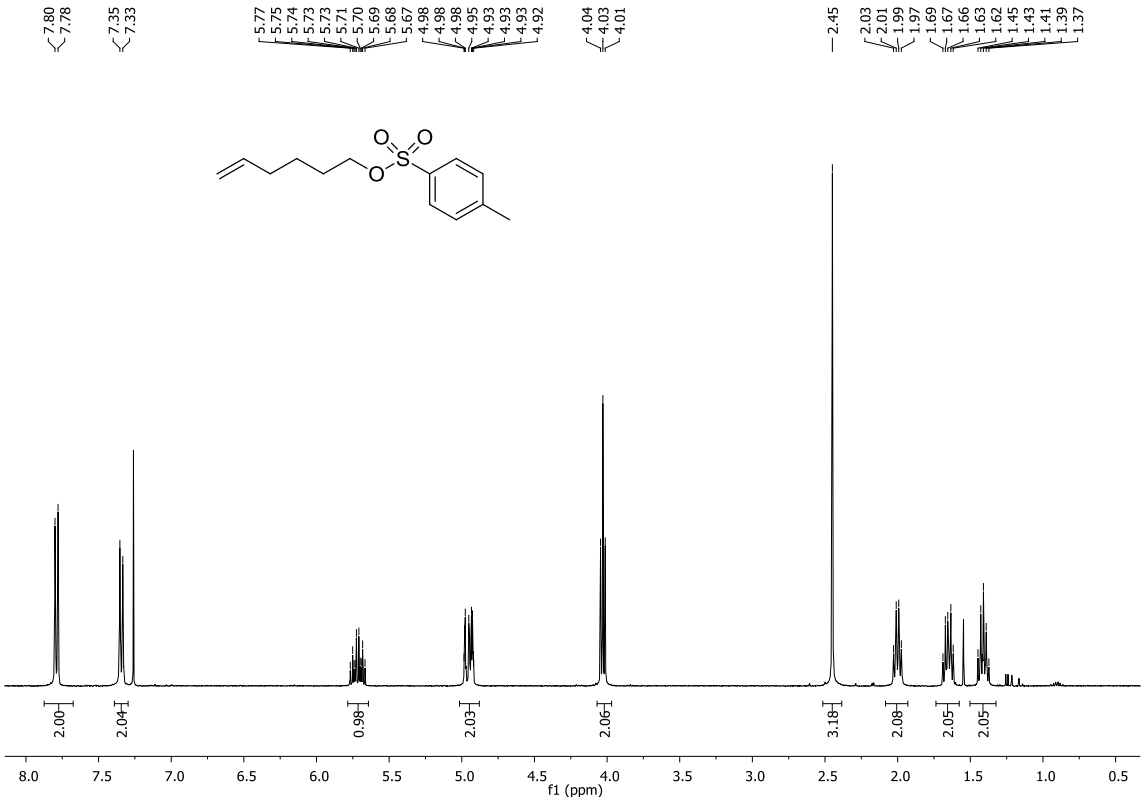
^{1}H NMR (400 MHz, $CDCl_3$) - **280**



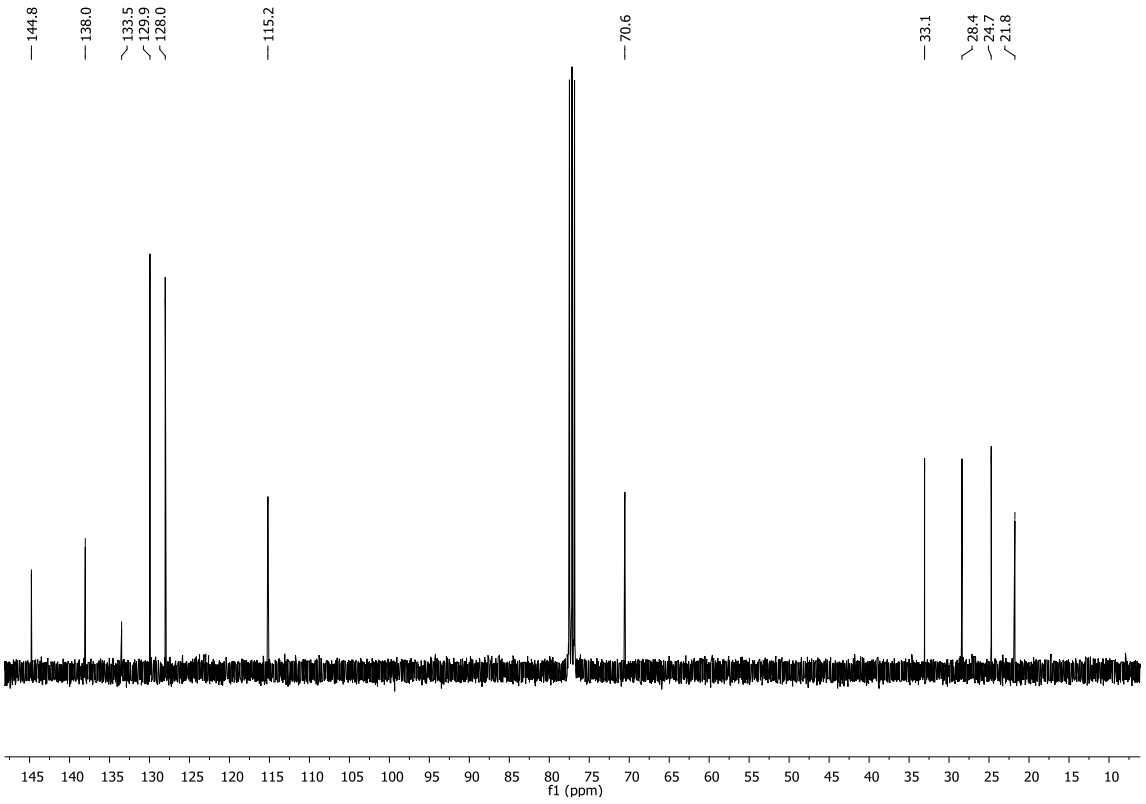
^{13}C NMR (101 MHz, $CDCl_3$) – **280**



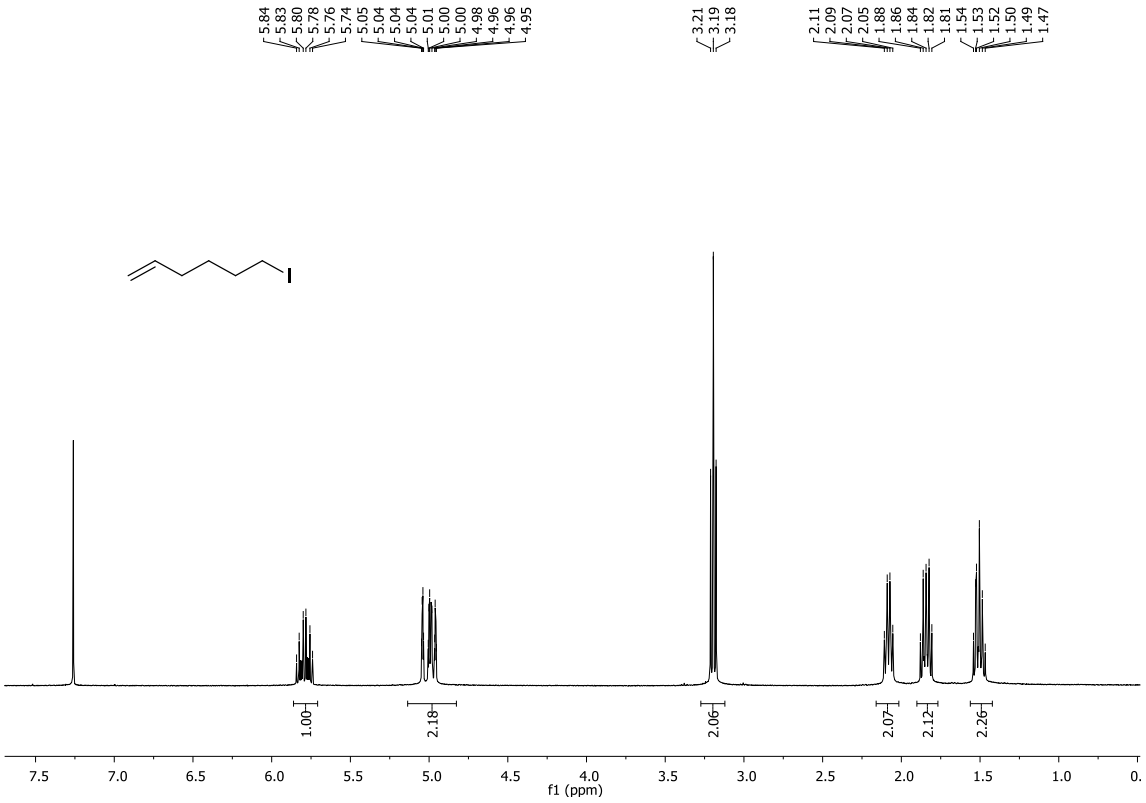
^{1}H NMR (400 MHz, $CDCl_3$) - **282**



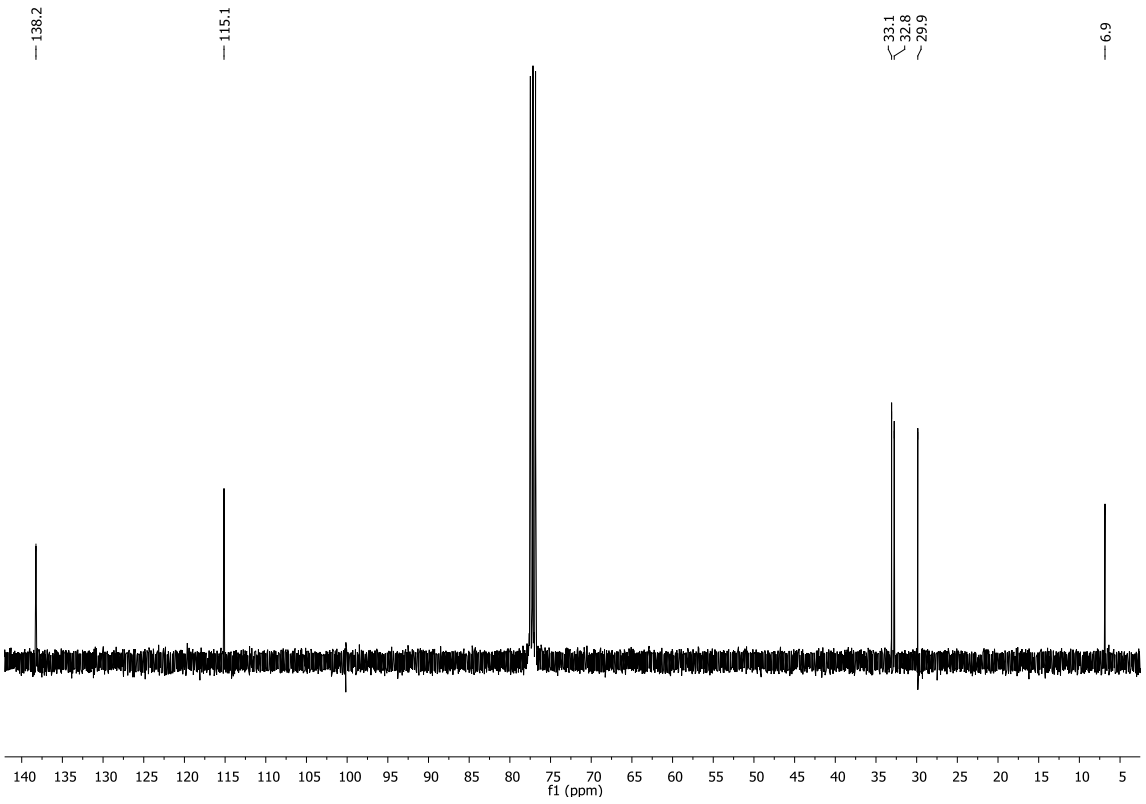
^{13}C NMR (101 MHz, $CDCl_3$) - **282**



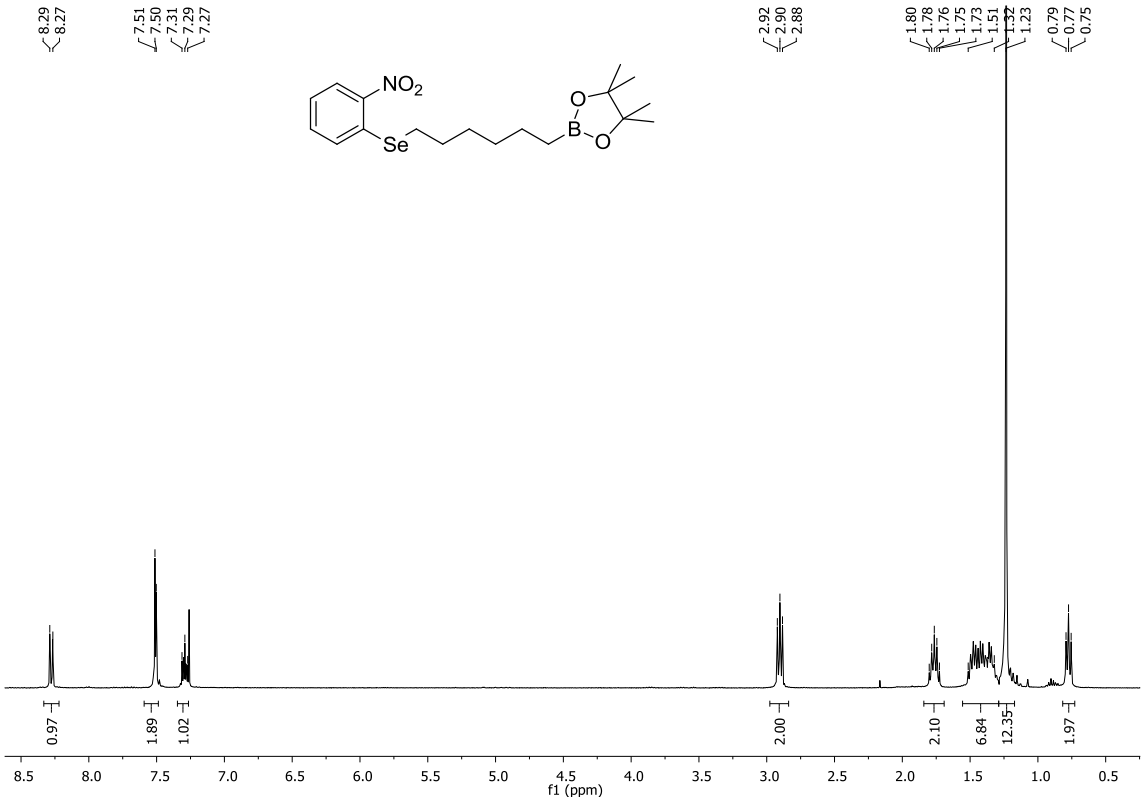
^{1}H NMR (400 MHz, $CDCl_3$) - **283**



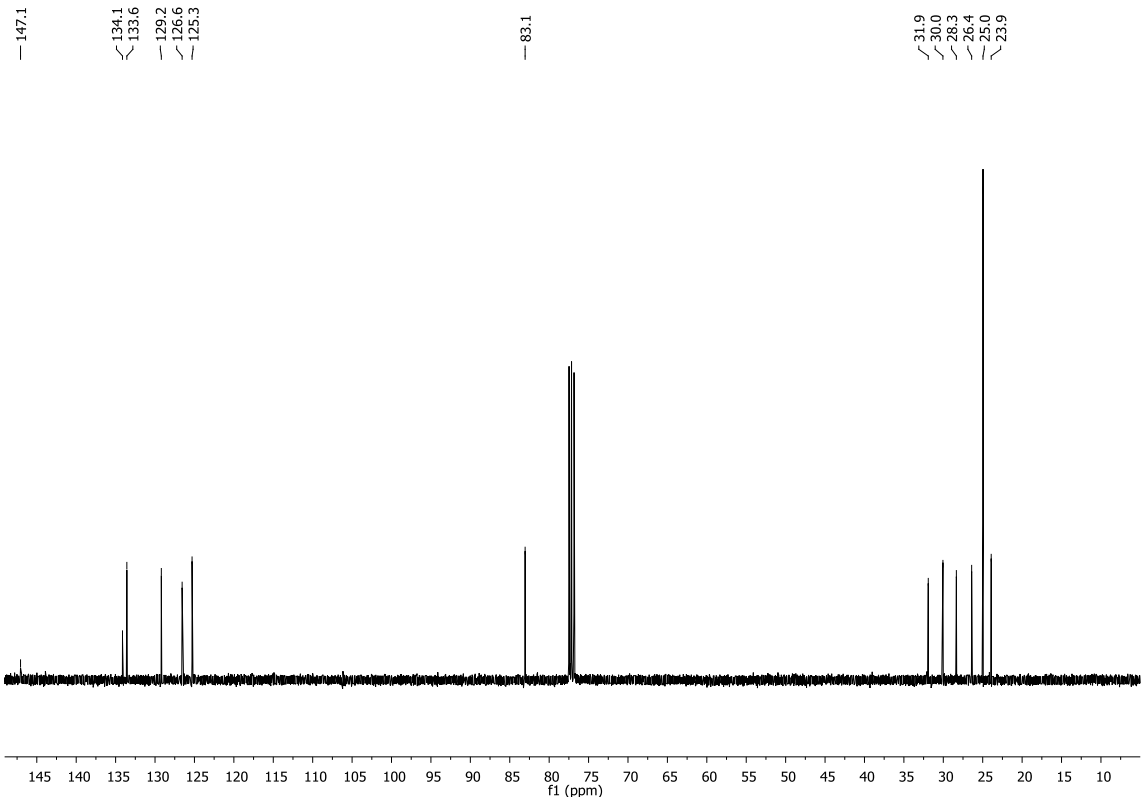
^{13}C NMR (101 MHz, $CDCl_3$) - **283**



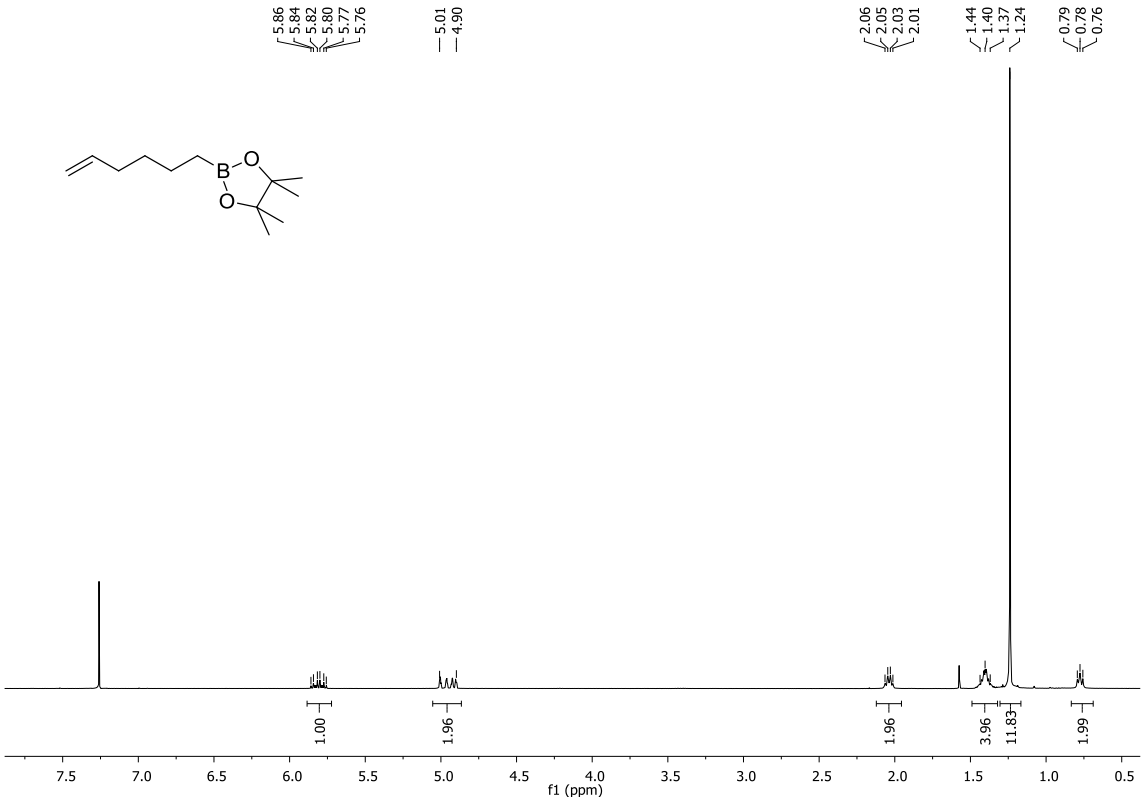
^{1}H NMR (400 MHz, $CDCl_3$) - **284**



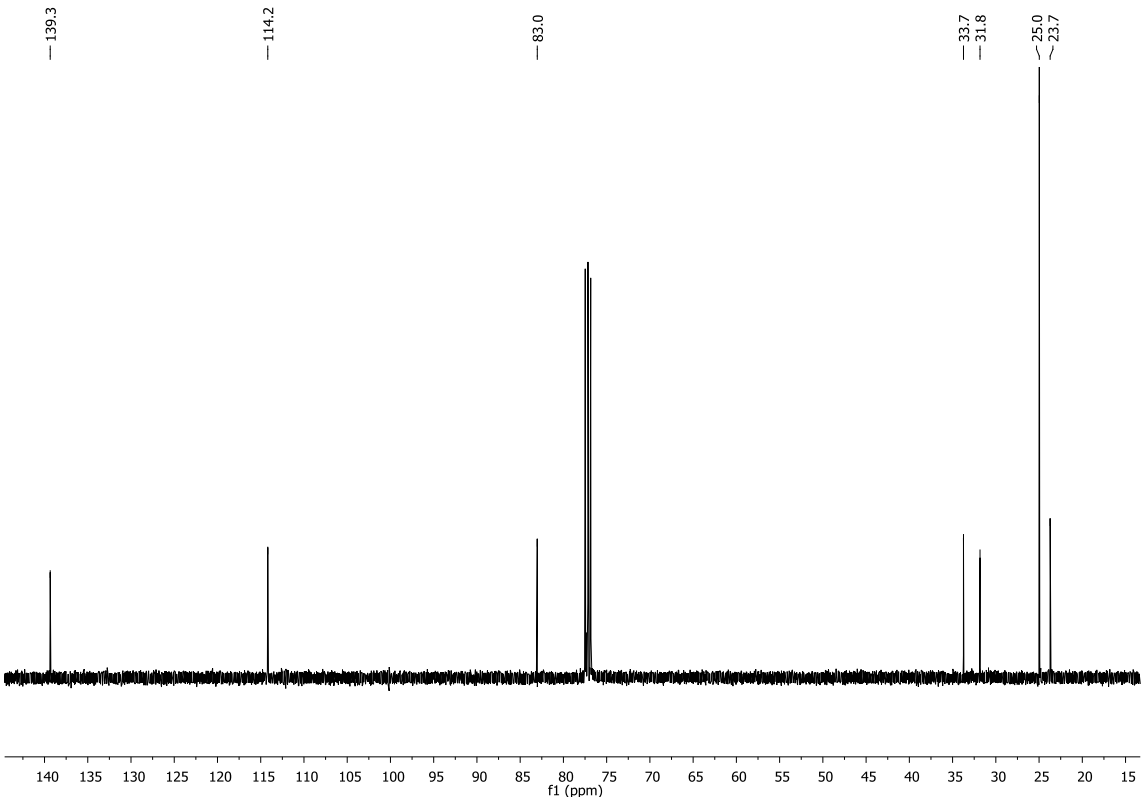
^{13}C NMR (101 MHz, $CDCl_3$) – **284**



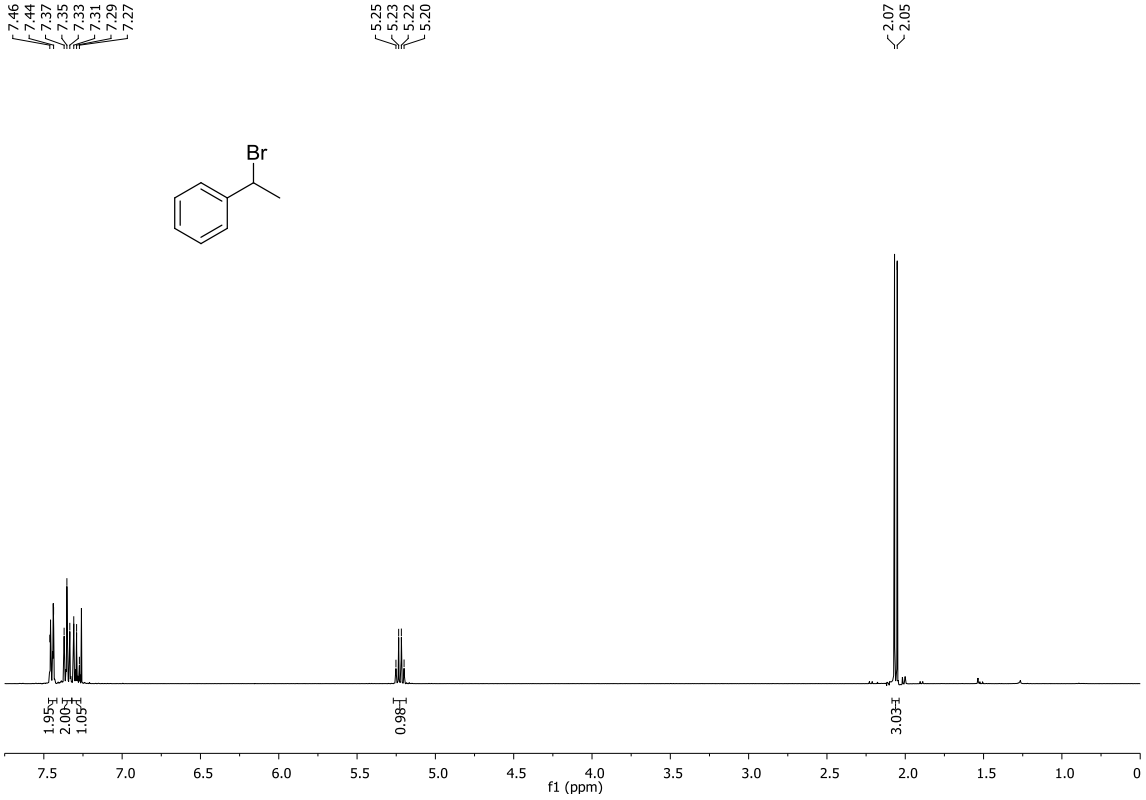
^{1}H NMR (400 MHz, $CDCl_3$) - **279**



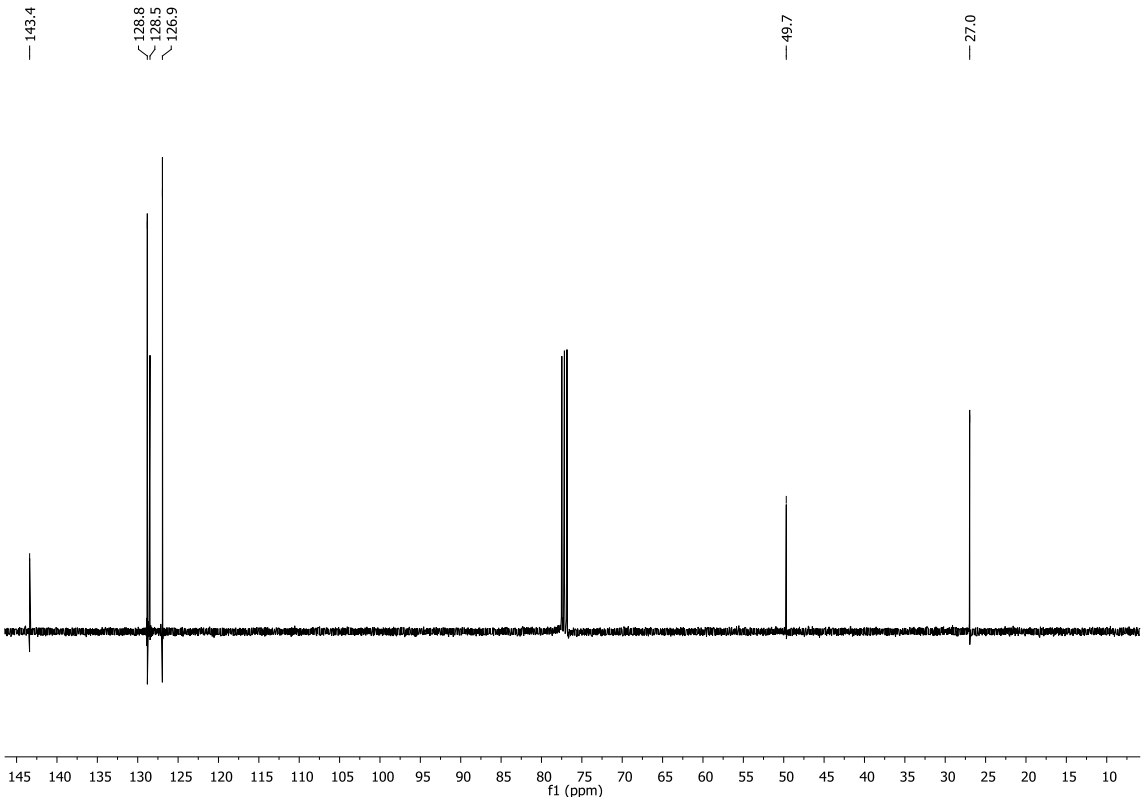
^{13}C NMR (101 MHz, $CDCl_3$) – **279**



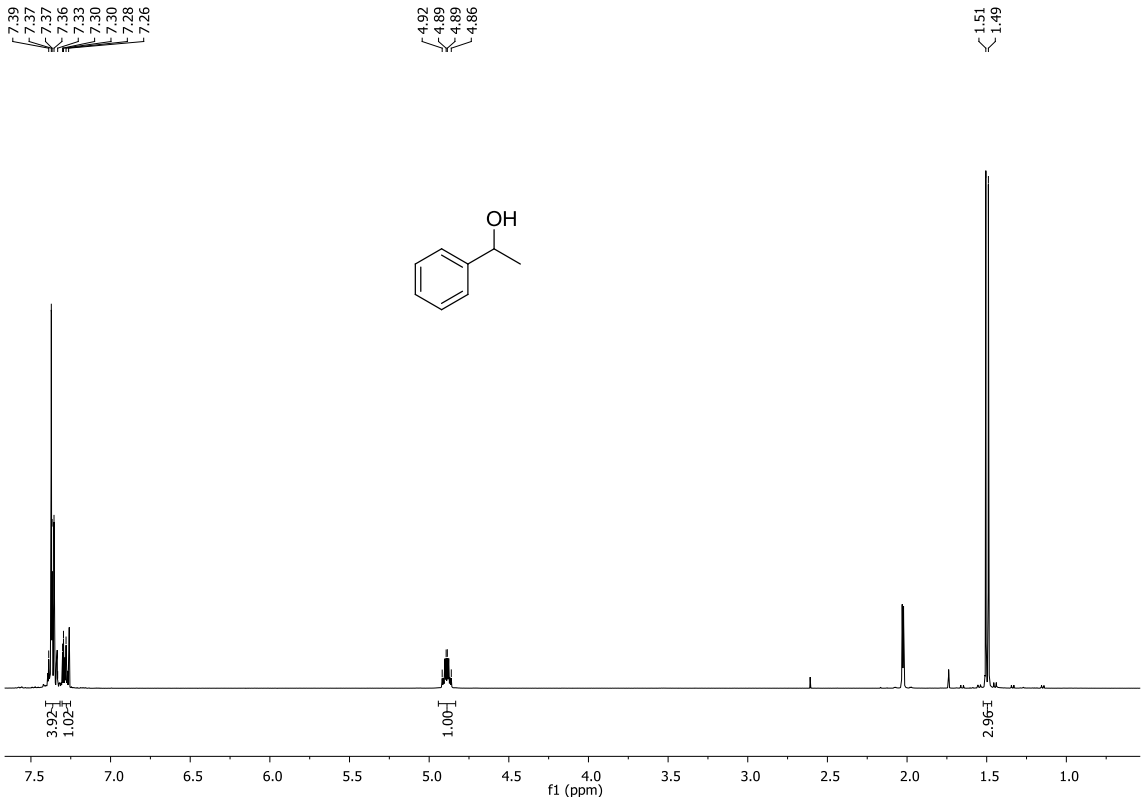
^{1}H NMR (400 MHz, $CDCl_3$) - **292**



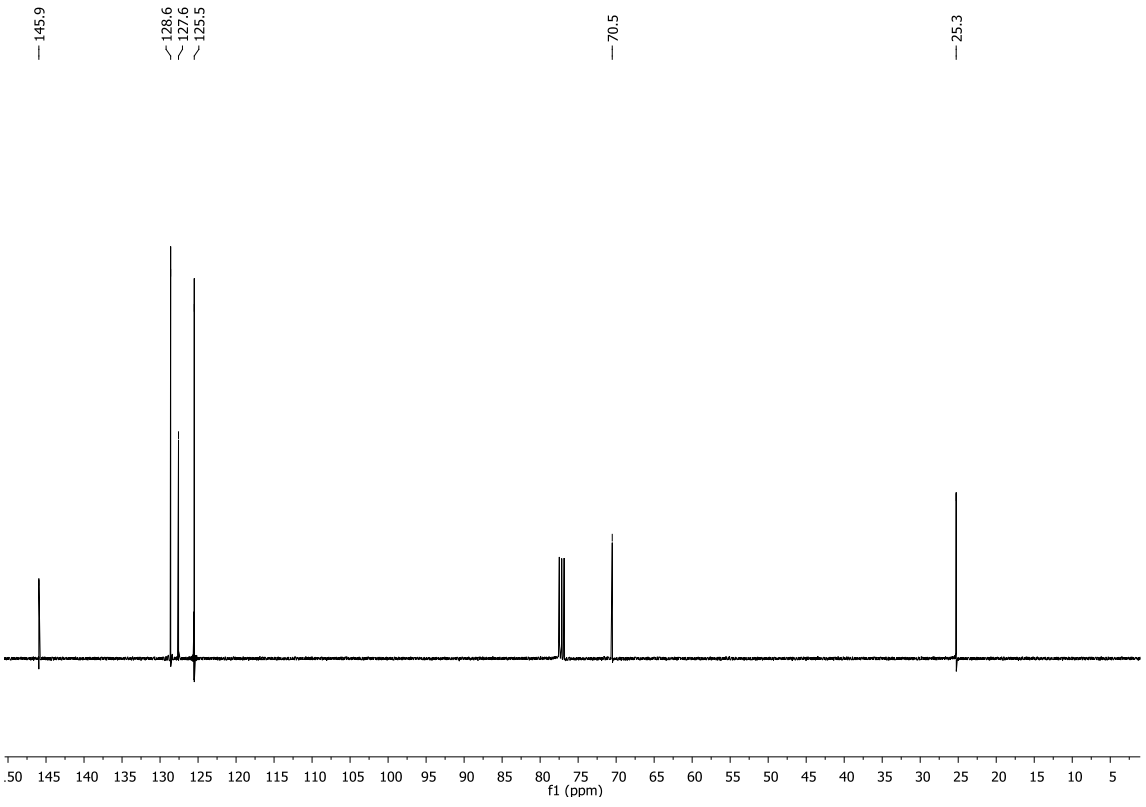
^{13}C NMR (101 MHz, $CDCl_3$) – **292**



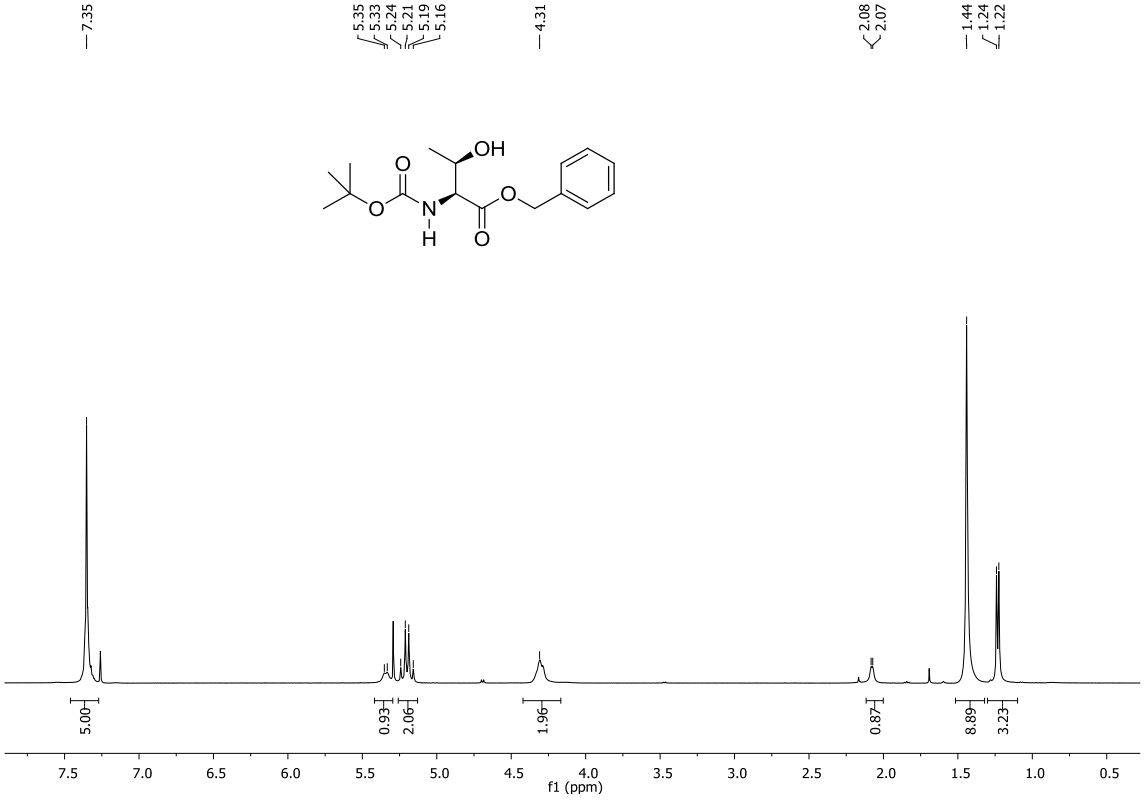
^{1}H NMR (400 MHz, $CDCl_3$) - **291**



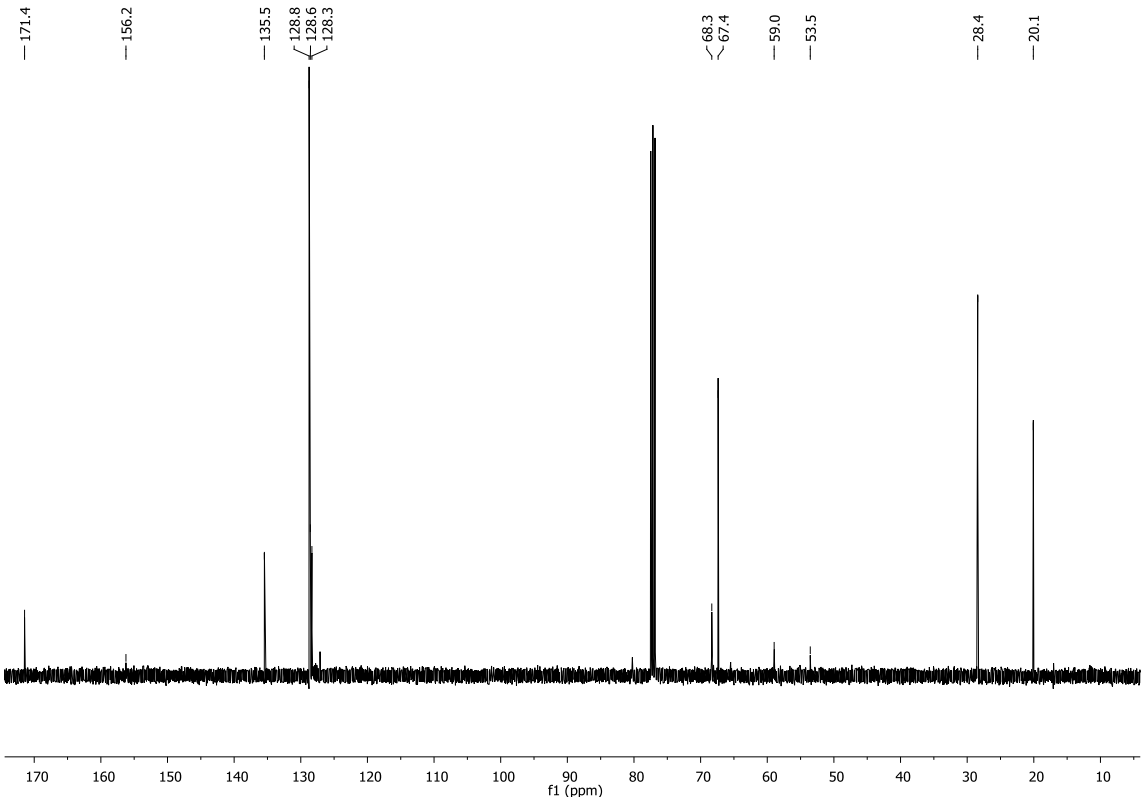
^{13}C NMR (101 MHz, $CDCl_3$) – **291**



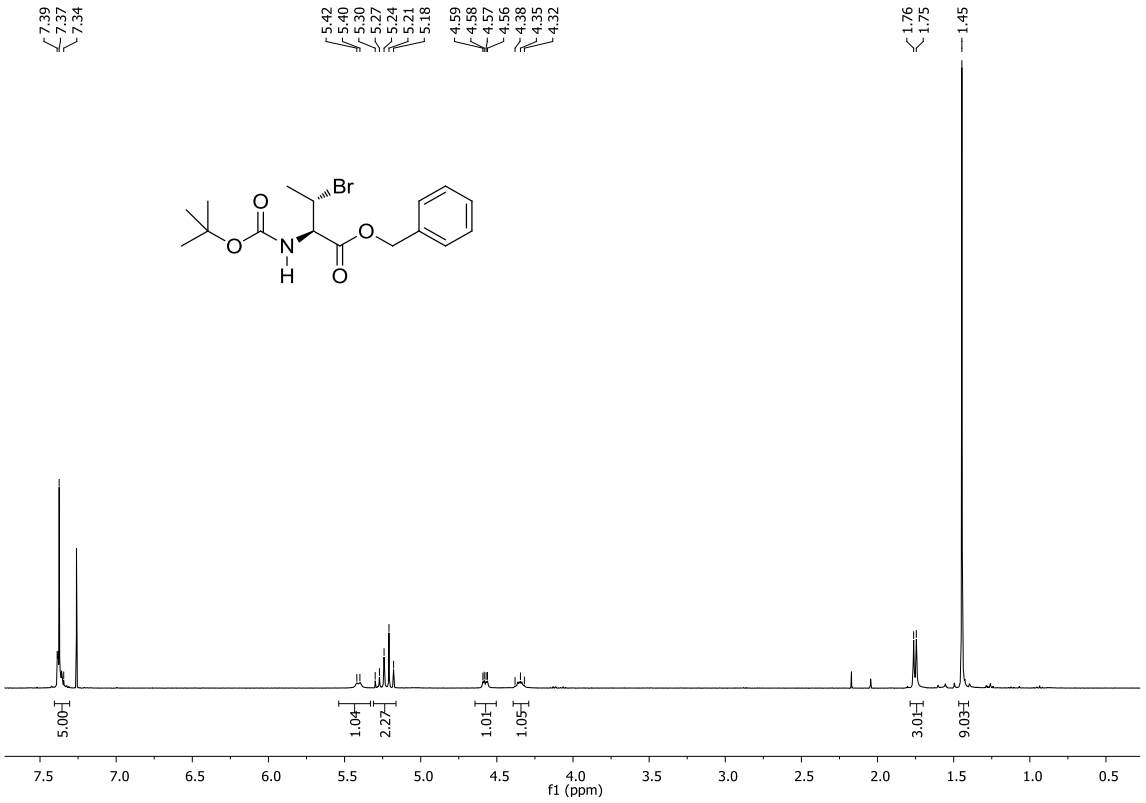
^{1}H NMR (400 MHz, $CDCl_3$) – **303**



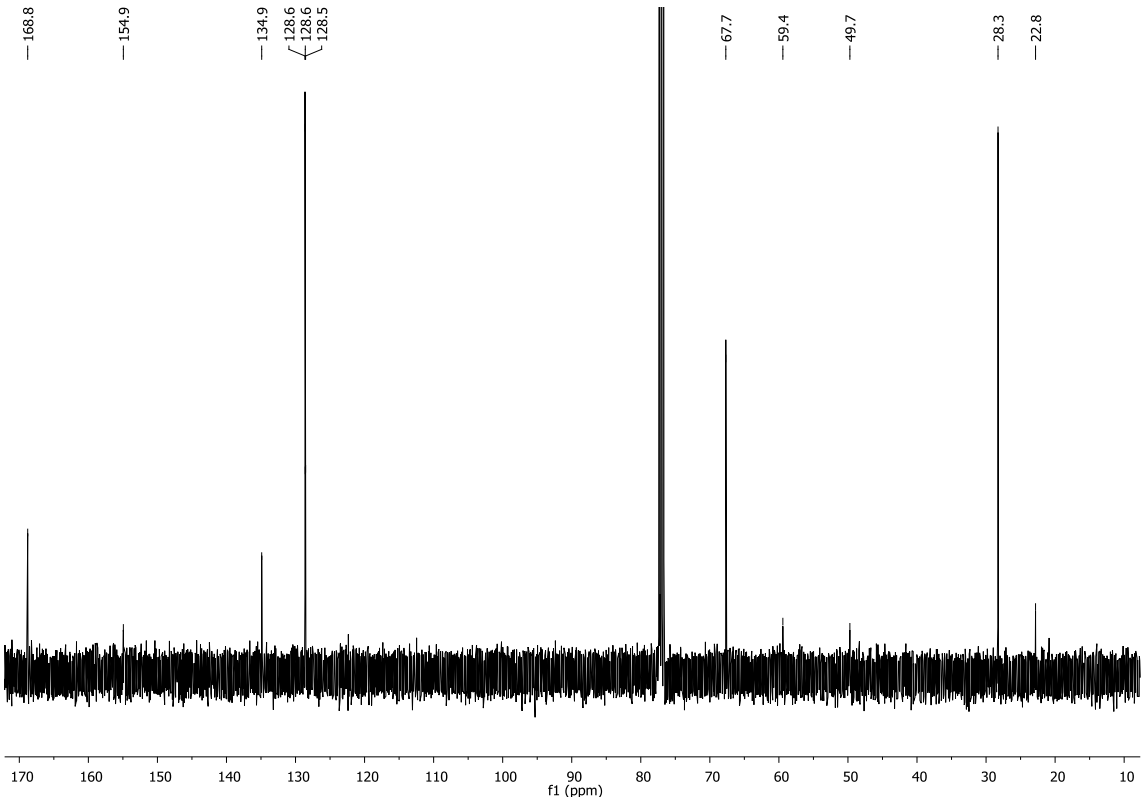
^{13}C NMR (101 MHz, $CDCl_3$) – **303**



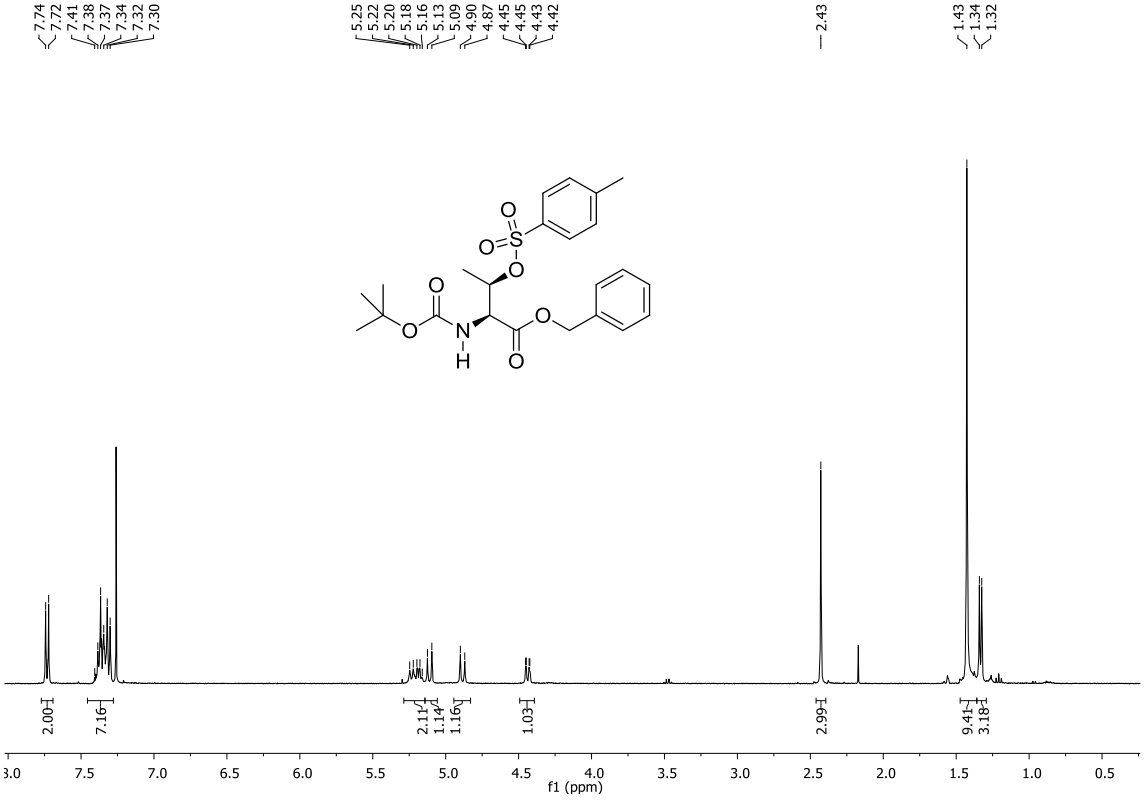
^{1}H NMR (400 MHz, $CDCl_3$) – **304**



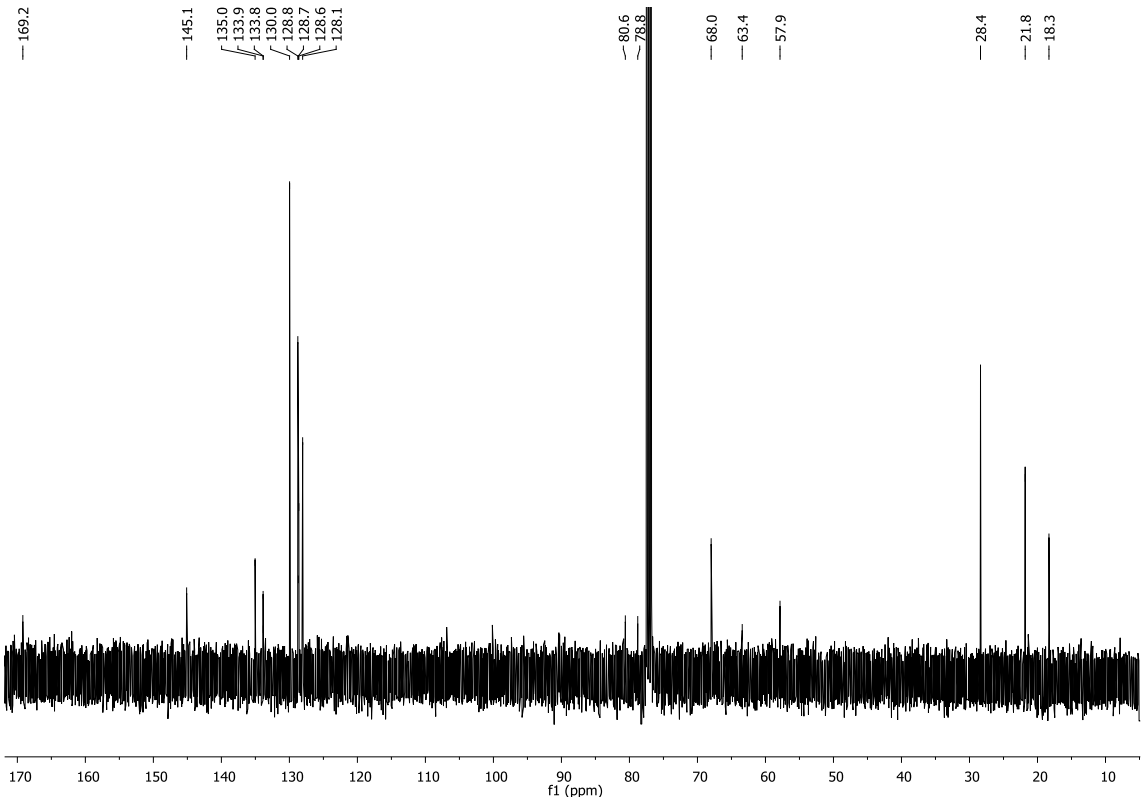
^{13}C NMR (101 MHz, $CDCl_3$) – **304**



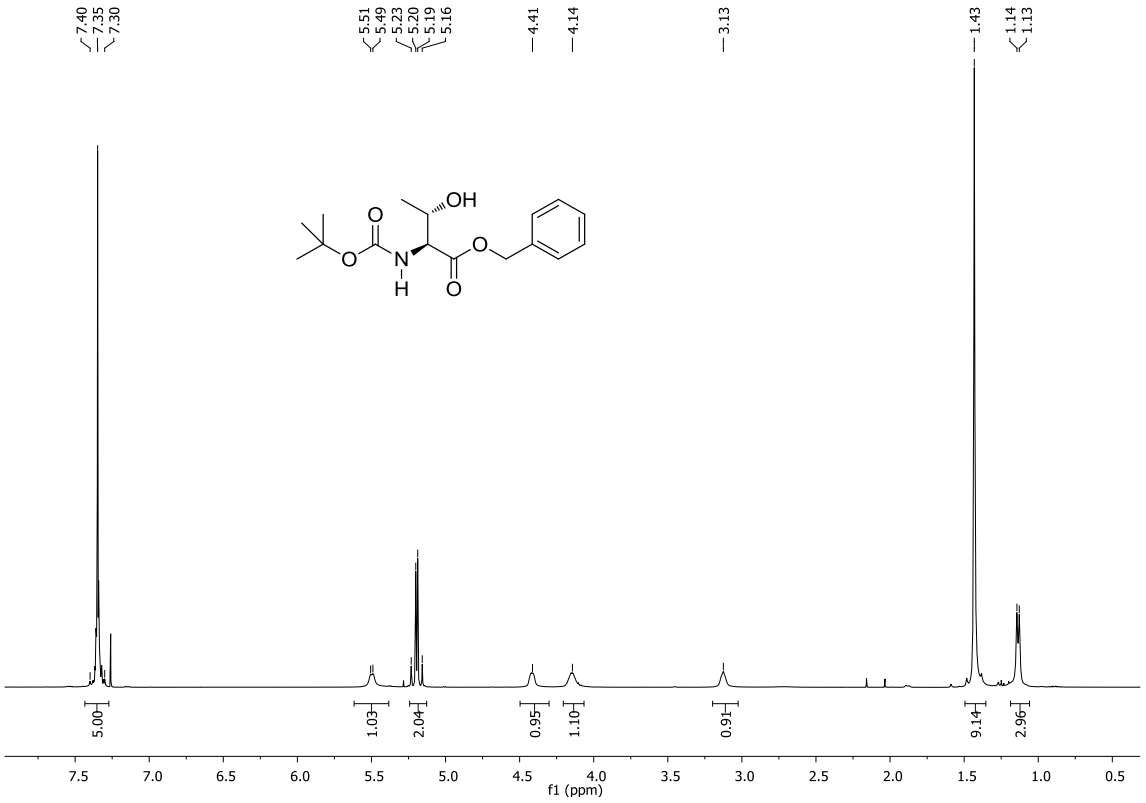
^{1}H NMR (400 MHz, $CDCl_3$) – **308**



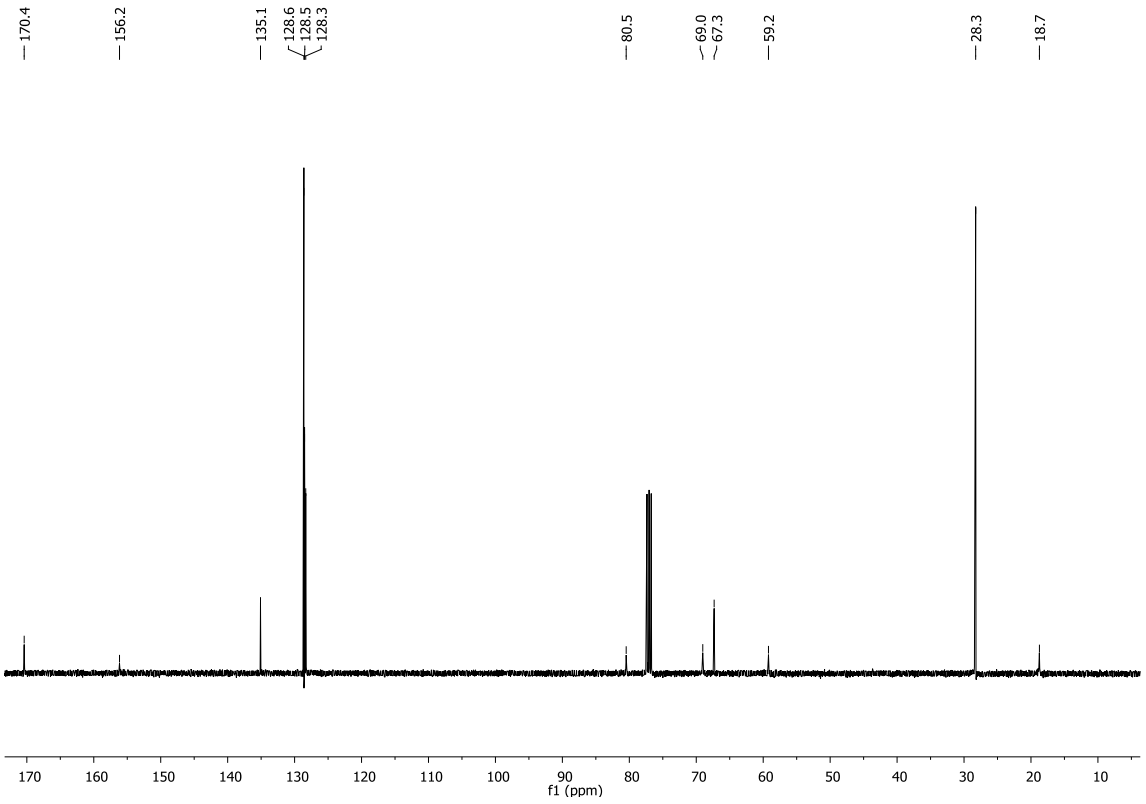
^{13}C NMR (101 MHz, $CDCl_3$) – **308**



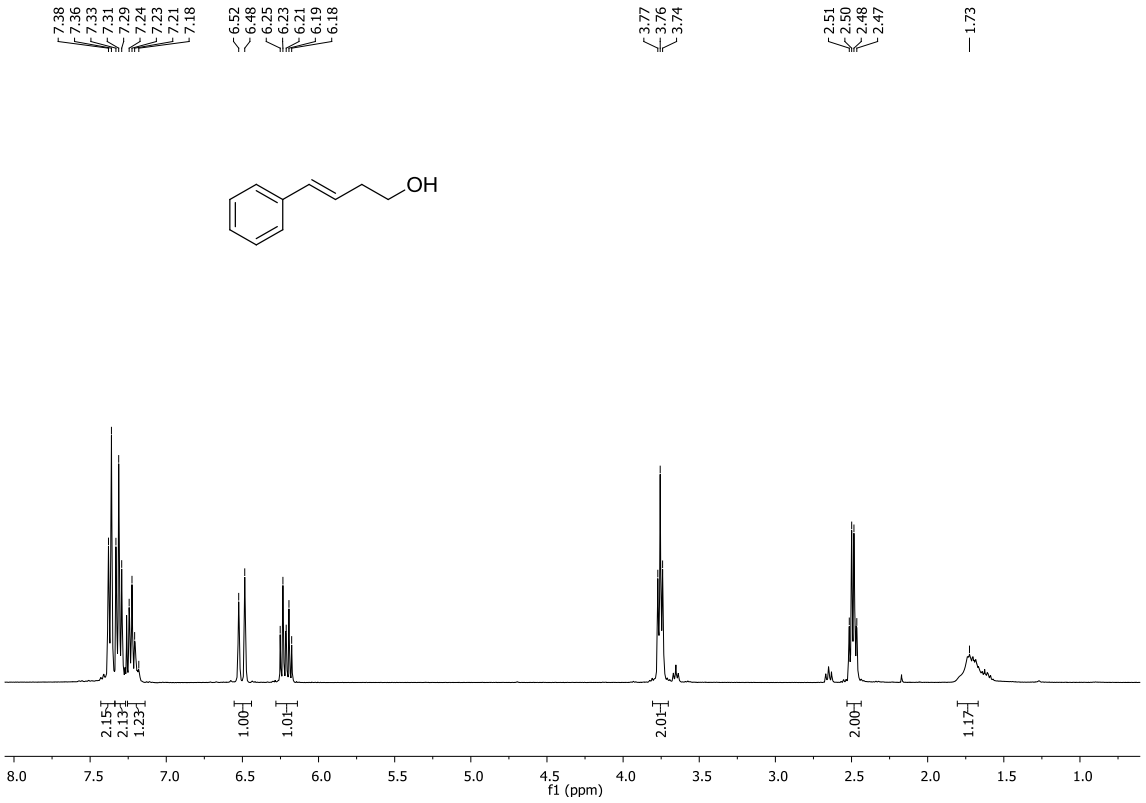
^{1}H NMR (400 MHz, $CDCl_3$) – **307**



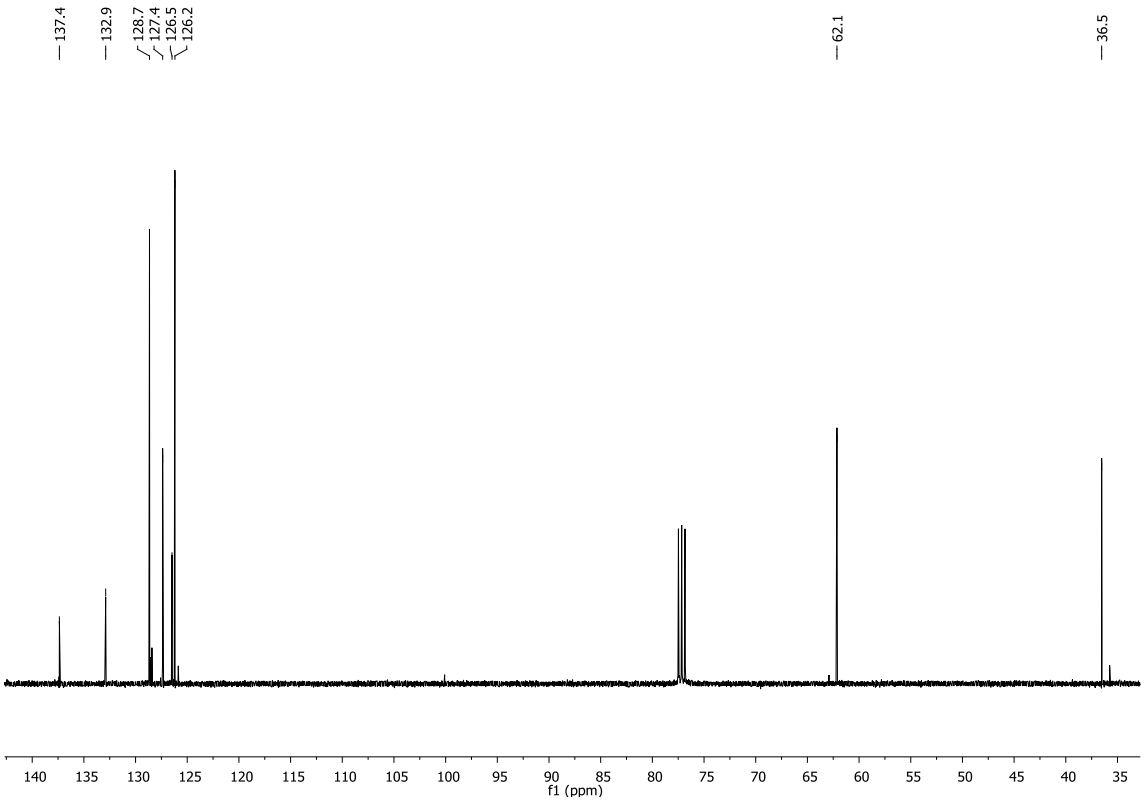
^{13}C NMR (101 MHz, $CDCl_3$) – **307**



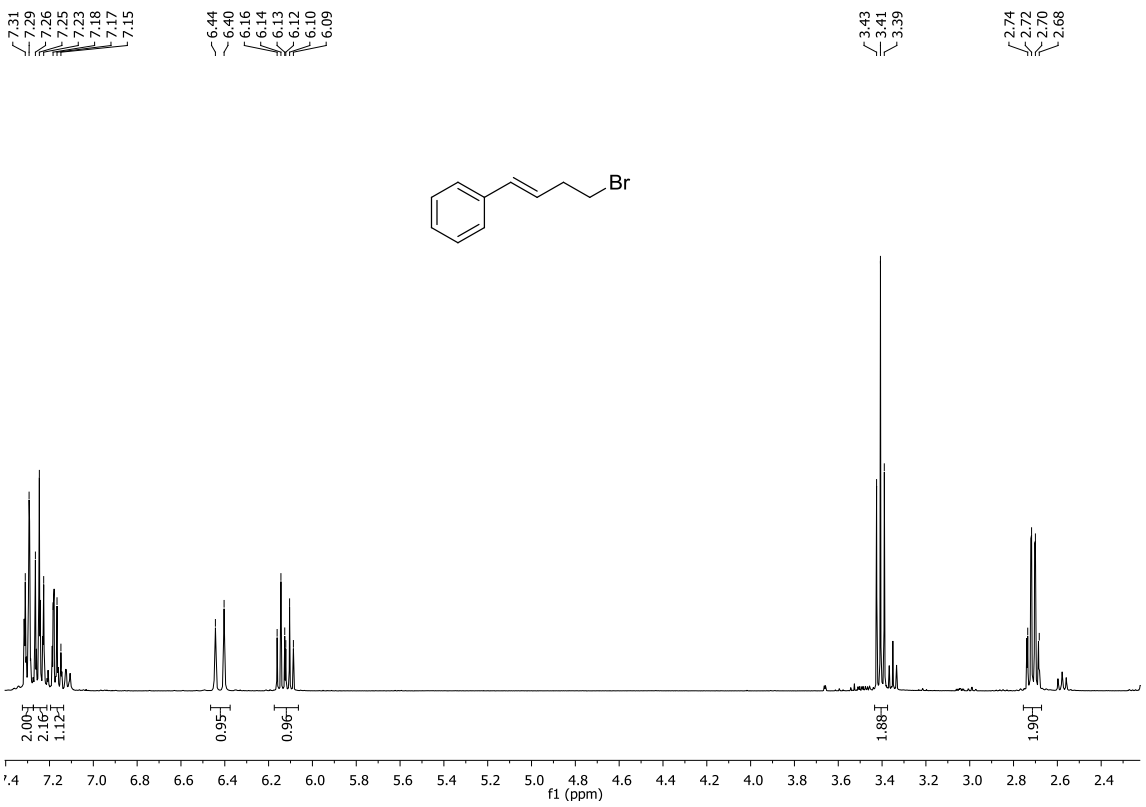
^{1}H NMR (400 MHz, $CDCl_3$) - **310**



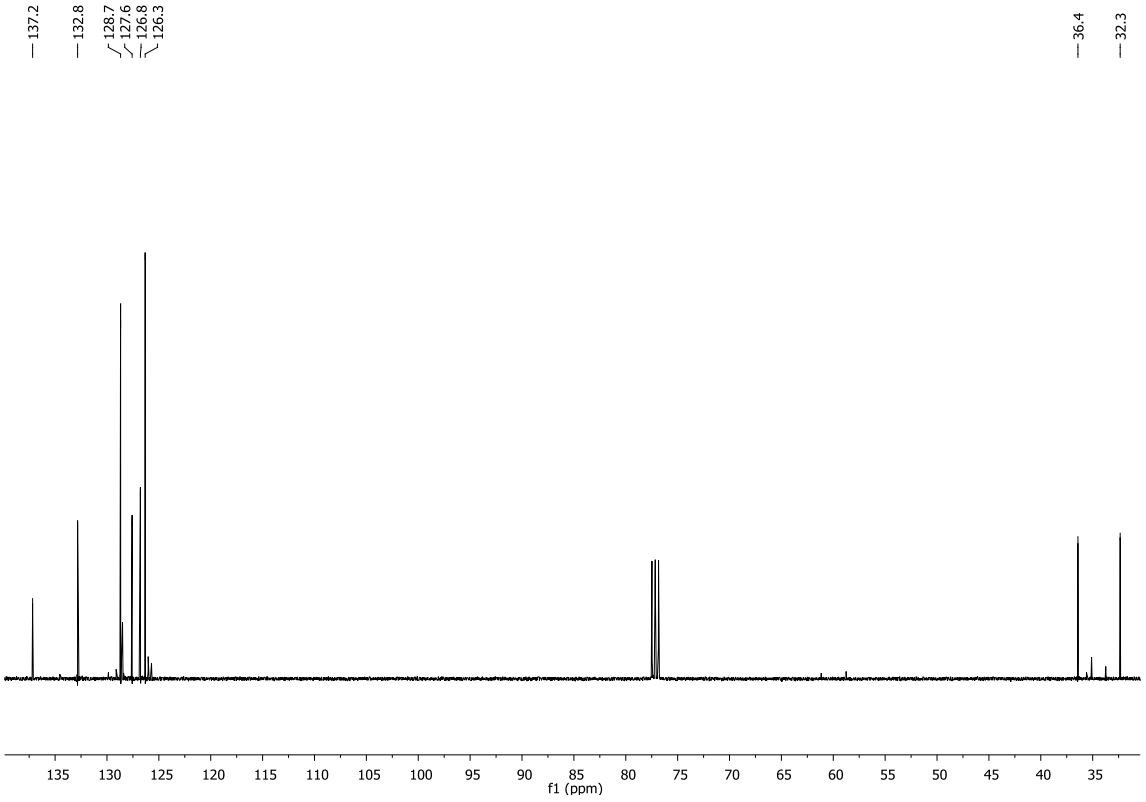
^{13}C NMR (101 MHz, $CDCl_3$) – **310**



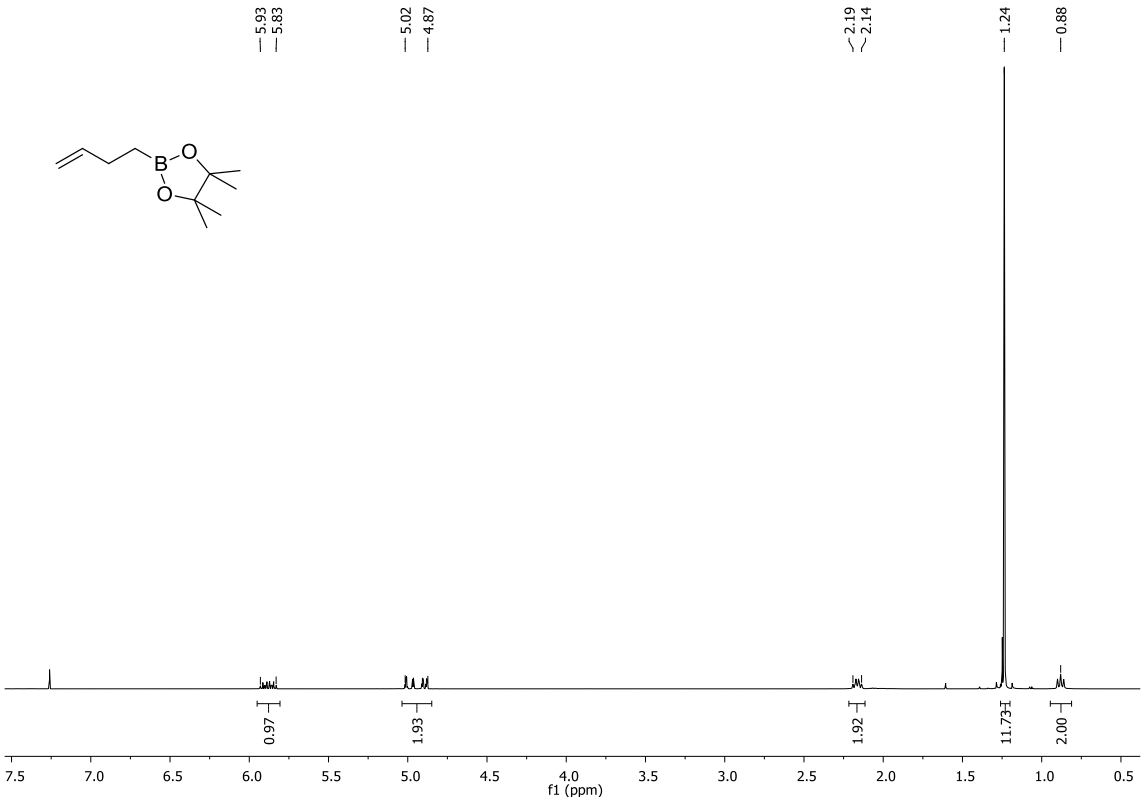
^{1}H NMR (400 MHz, $CDCl_3$) - **311**



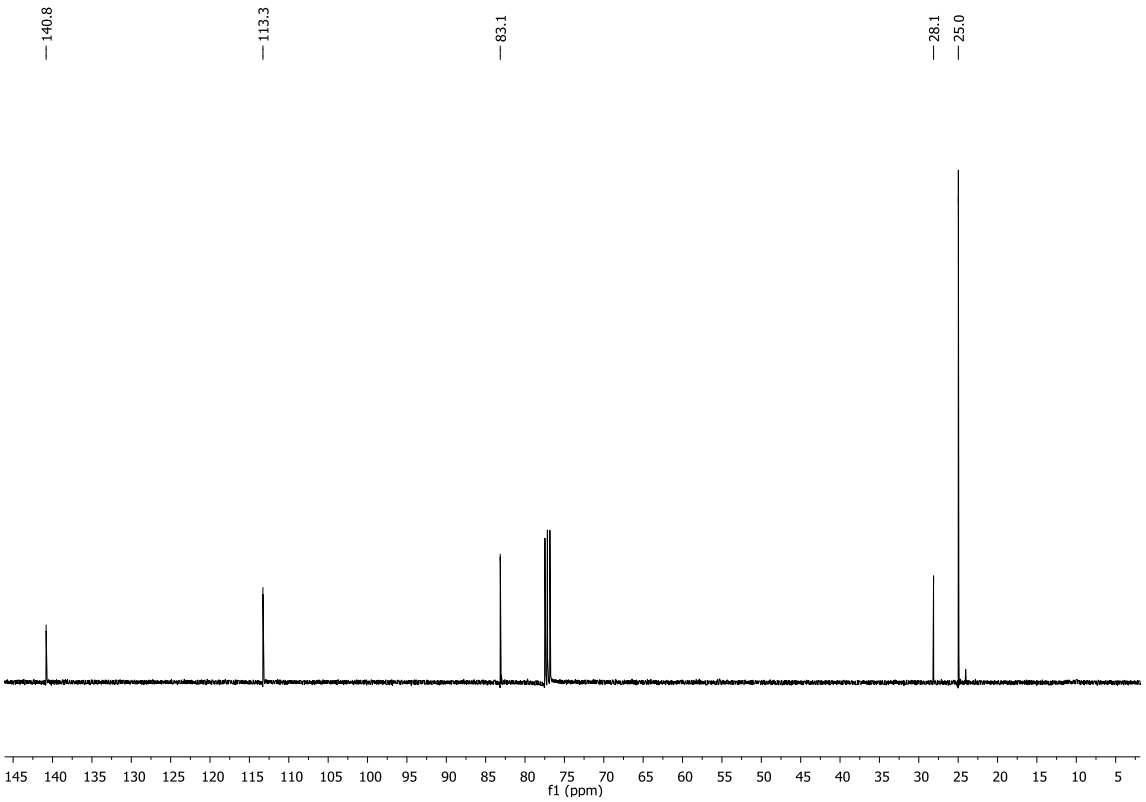
^{13}C NMR (101 MHz, $CDCl_3$) – **311**



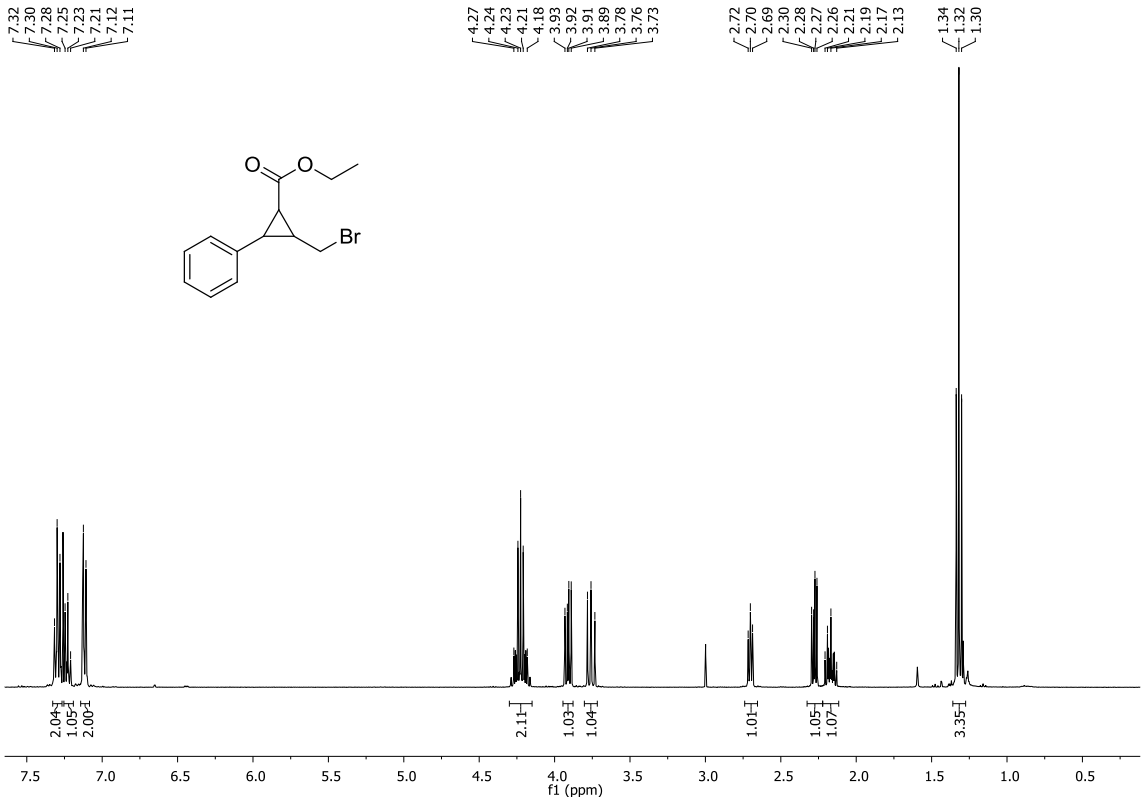
^{1}H NMR (400 MHz, $CDCl_3$) - **314**



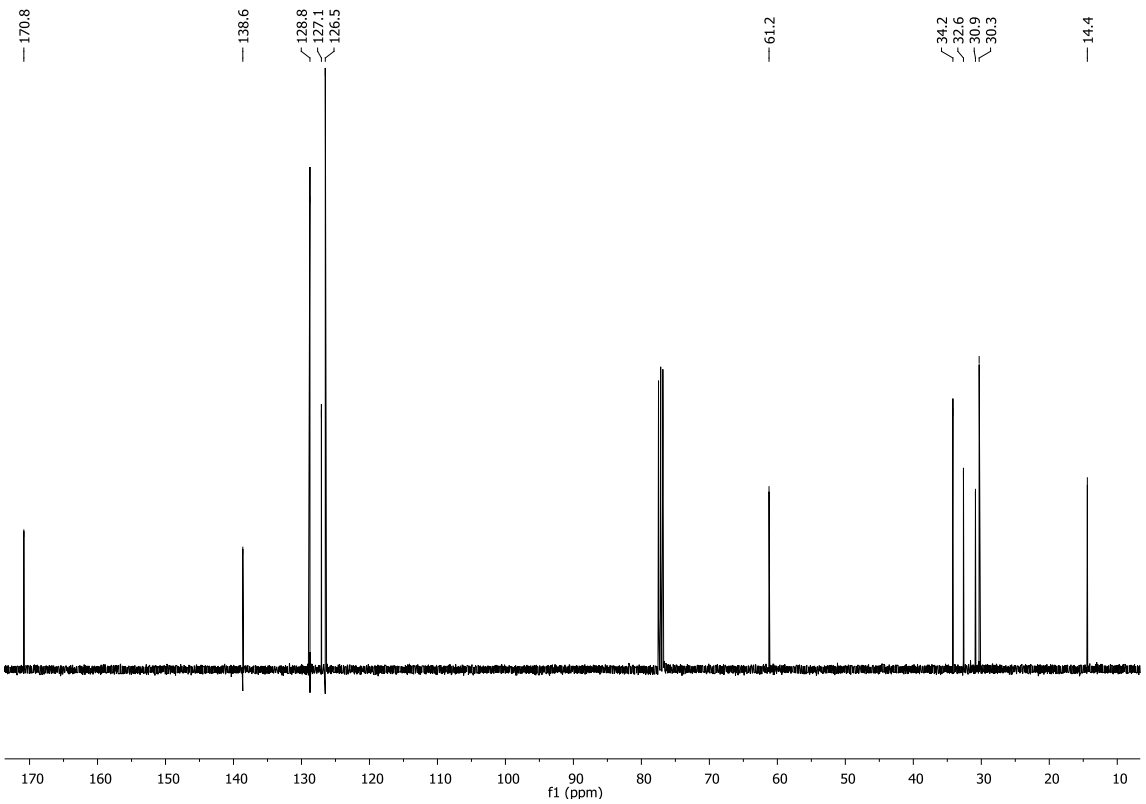
^{13}C NMR (101 MHz, $CDCl_3$) – **314**



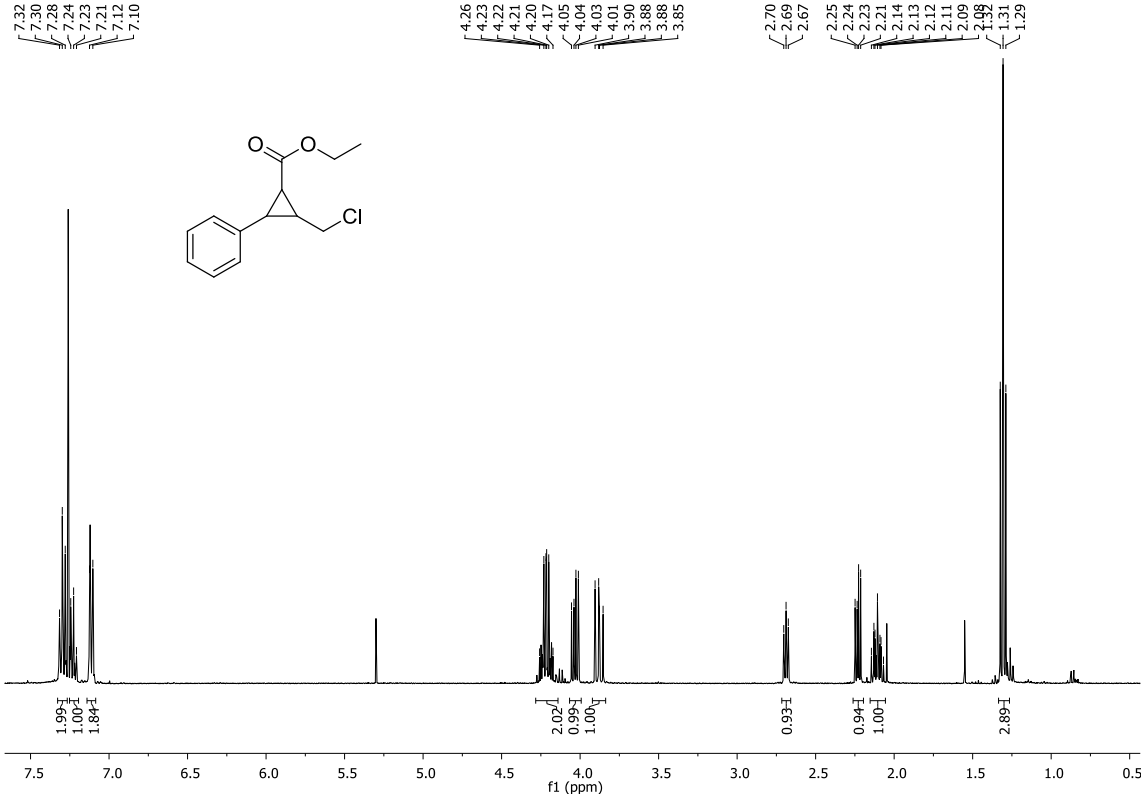
^{1}H NMR (400 MHz, $CDCl_3$) - **318**



^{13}C NMR (101 MHz, $CDCl_3$) – **318**



^{1}H NMR (400 MHz, $CDCl_3$) - **319**



^{13}C NMR (101 MHz, $CDCl_3$) – **319**